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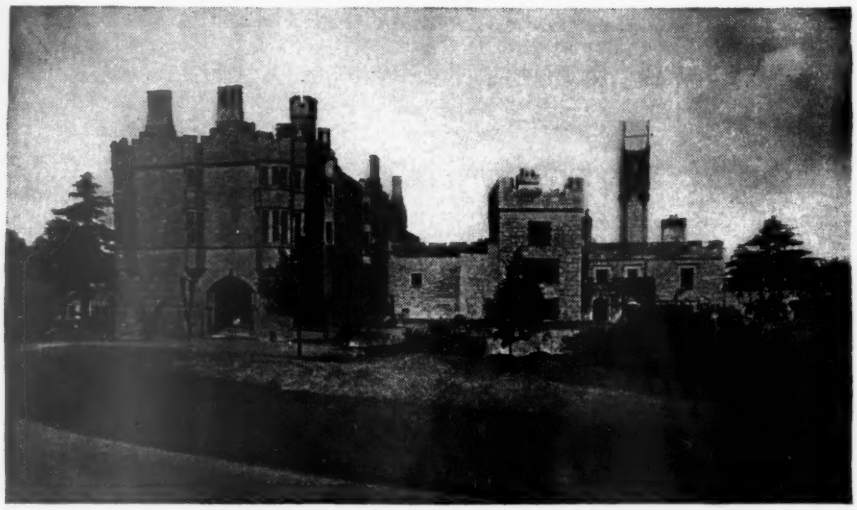

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SCHÖNLEIN-HENOCH PURPURA[1]

Evidence for a Group A β-Haemolytic Streptococcal Aetiology

By E. G. L. BYWATERS, I. ISDALE, and J. J. KEMPTON

(From the Canadian Red Cross Memorial Hospital, Taplow, Bucks., the Postgraduate Medical School, London, and the Royal Berkshire Hospital, Reading, Berks.)

With Plates 20 and 21

Gairdner (1948), in a comprehensive and detailed study of 12 cases of Schönlein-Henoch purpura from Newcastle-on-Tyne, called attention to the close relationship this disease bears to acute nephritis and to rheumatic fever, both of which are now accepted as being due to a preceding group A β-haemolytic streptococcus infection. Thus one of his patients developed rheumatic carditis, and subsequently had mitral and aortic disease and cardiac enlargement. Another at post-mortem examination showed renal changes indistinguishable from subacute glomerulonephritis. In general, however, proven rheumatic carditis is very rare in rheumatic purpura (Osler, 1914), and purpura is rare in rheumatic fever. Among more than 1,000 cases of rheumatic fever we have seen one case in which purpura occurred on the arms; but this was after sphygmomanometer readings, and we have not thought it to be a case of Schönlein-Henoch purpura. Systolic murmurs have often been misinterpreted, and even a soft basal diastolic murmur, which has been heard on one occasion in three of our present 52 cases, is not by itself indicative of rheumatic fever. The nephritis of Schönlein-Henoch purpura is in a different category: both the clinical and the histological features are closely similar to those of glomerulonephritis. The evidence, however, for the streptococcal aetiology of rheumatic fever and glomerulonephritis rests upon two main sets of data: the isolation of group A β-haemolytic streptococci from the throat during or before the attack, and the demonstration of a raised antibody titre in the serum. Neither of these data have been provided for Schönlein-Henoch purpura. Gairdner isolated the 'haemolytic streptococcus' from 'a majority' of his patients (? five out of six), as well as from all six of a later series, but the organisms were not grouped, and no antibody determinations were made. Other authors, for example, Lewis (1955), have also stressed the similarity between these three diseases as regards sex ratio, seasonal incidence, preceding upper respiratory infection, latent period, and isolation of a haemolytic streptococcus, but few have grouped these streptococci, and none have recorded the antibody responses. We have, therefore,

[1] Received June 2, 1956.

studied from this viewpoint all the patients fulfilling designated criteria for Schönlein-Henoch purpura who have been admitted to the Canadian Red Cross Memorial Hospital in the past seven years; in most of them cultures were made from weekly throat and nose swabs and serum was examined for anti-streptolysin O (A.S.O.). Because this is a National Centre for Juvenile Rheumatism and might possibly attract an unusual type of case, and to ascertain whether the cases investigated here were fully representative of the syndrome, we have compared the clinical findings with those obtained in a series of 24 patients fulfilling the same diagnostic criteria and admitted to the Royal Berkshire Hospital under the care of one of the authors (J. J. K.) during the same period. Some further data have been obtained regarding a few patients admitted to the Postgraduate Medical School. Finally, a comparison, as regards antibody levels and culture of group A β-haemolytic streptococci, has been made with a series of non-rheumatic control children of the same age, and with a series of children with rheumatic fever, since in most series the A.S.O. titre has been found to be raised in only 80 per cent. of patients with rheumatic fever (Swift, 1949).

Patients Studied and Methods

All patients admitted to the Canadian Red Cross Memorial Hospital since April 1948 in whom purpuric rash was seen in hospital, or in whom a reliable history of such rash was obtained, have been reviewed. While it is probable that cases of Schönlein-Henoch purpura occur which show only one manifestation of the syndrome, only those patients with purpura have been included who showed in addition, at some time during the attack, at least one of the following manifestations: localized oedema, abdominal symptoms, joint involvement, or renal involvement. Patients showing such a combination of signs, but with other diagnoses such as subacute bacterial endocarditis, Waldenström purpura, disseminate lupus erythematosus, glandular fever, Werlhof's disease, or leukaemia, have been excluded. In most cases which fulfilled the above criteria platelet counts and bleeding-time and coagulation-time estimations were made, and all the results were within normal limits.

Attention has been directed particularly to the incidence of raised A.S.O. titres, the actual A.S.O. levels, the frequency of preceding infection of the upper respiratory tract within a month of onset, and the frequency with which group A β-haemolytic streptococci were recovered from the nose and throat on admission or within one week thereof. In cases seen at the Special Unit for Juvenile Rheumatism throat and nose swabs were taken from each patient on admission and after one week, and were plated on blood-agar and on the same medium containing gentian violet (1:500,000). Haemolytic streptococci found were tested for group-A-specific polysaccharide by Lancefield's method (1933), and were typed when possible by the precipitin method (Swift, Wilson, and Lancefield, 1943). Serum A.S.O. estimations were made on admission, and subsequently at weekly intervals, by our own modifications (Johnson, 1955) of Todd's method as used by Hodge and Swift (1933). This method was stan-

dardized by reference to Todd's horse antiserum. For comparative purposes, all patients with acute rheumatic fever within the same age-group, and a second similar group of children admitted during a period of three years with conditions unrelated to the rheumatic diseases, both in the Special Unit at Taplow, have been analysed with regard both to the incidence of preceding infection of the upper respiratory tract and to the incidence, on admission, of isolation of group

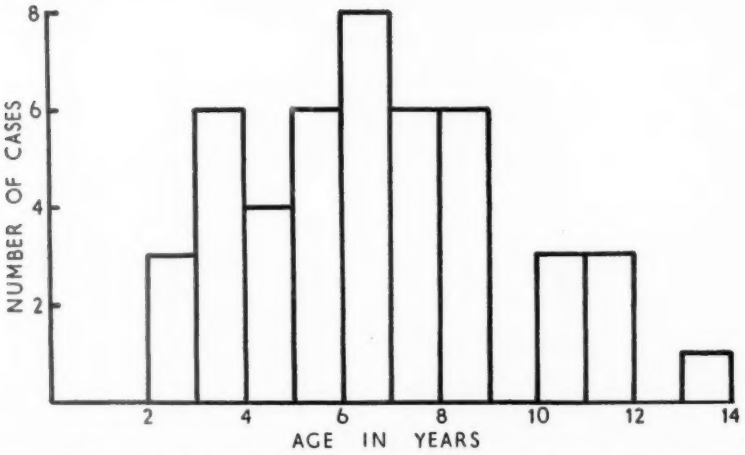

FIG. 1. Distribution of ages at onset in 46 cases of Schönlein-Henoch purpura. In six other cases included in the series the onset was between the ages of 20 and 57; these are not shown in the figure.

A β-haemolytic streptococci and raised A.S.O. titre. In patients seen at the Royal Berkshire Hospital no estimations of A.S.O. were made, and evidence of haemolytic streptococcal infection was sought in only a minority of cases, but otherwise the analysis has been comparable. Thirteen patients seen at the Postgraduate Medical School, and satisfying the above criteria of Schönlein-Henoch purpura, have also been reviewed in relation to streptococcal aetiology, A.S.O. titres being estimated in 10.

Results

During the seven-year period of the survey 28 patients seen in the Canadian Red Cross Memorial Hospital fulfilled the criteria for admission to the series. Of these 23 were under the age of 12 years; the remaining five were aged 20, 28, 30, 47, and 57 years at onset. In the same period 24 patients were seen at the Royal Berkshire Hospital; only two of these were over the age of 12 years (aged 14 and 40 respectively). The greatest incidence in both groups was between the ages of five and seven years; the age-distribution of the combined series is shown in Fig. 1. The seasonal incidence of onset was similar in both groups (Fig. 2), being greatest in February and October, as has been noted by Lewis (1955).

The sex incidence was approximately equal at both hospitals (Table I). This finding is in keeping with the observation of Simpkiss (1953) who analysed a group of cases in children, but in contrast to the increased incidence in male patients reported by Gairdner (1948). Four of the 52 patients, all children, had a second attack at periods varying from two months to one year after the initial

TABLE I

Sex Incidence

	Present series				
	Canadian Red Cross Memorial Hospital	*Royal Berkshire Hospital*	*Total*	*Simpkiss (1953)*	*Gairdner (1948)*
Male . . .	14	11	25	27	85
Female . .	14	13	27	24	34
Total . .	28	24	52	51	119

attack, and one child experienced a third attack. Some cases ran a chronic relapsing course, with fresh crops of rash, localized oedema, arthritis, or haematuria, but for the purposes of the present survey such patients have been regarded as suffering from one attack unless there was a period of at least six weeks during which none of the diagnostic manifestations enumerated were present. The incidence of the five characteristic manifestations was comparable in the two hospital groups (Table II)

Rash. During the course of the 57 attacks (in 52 patients) rash was seen in all but one instance, the third attack of a five-year-old boy. The characteristic skin lesion is purpura, individual lesions being pink non-itching papulo-macules when they first appear, subsequently, within a few hours, flattening and becoming first dull red, then purple in colour, and finally fading after three or four days. Some brown staining may remain for as long as a week. While all patients in this survey showed such purpuric lesions, the first skin abnormality in 20 (35 per cent.) was urticaria, the purpura appearing later in the urticarial areas and subsequently undergoing the above changes in colour. This more acute onset of rash was not associated with a greater severity of the illness, nor with a worse prognosis. In a few cases petechiae or ecchymoses were seen in conjunction with purpura. In only one case was superficial skin necrosis seen. The skin lesions of Schönlein-Henoch purpura involve the extensor surfaces rather than the flexor aspects, and limbs far more than the trunk or head. In the present series they were usually roughly symmetrical. On all but three occasions rash was seen on the legs, and was usually most pronounced there. Rash on the buttocks, though often regarded as more typical, was seen less

often, in 42 out of 56 attacks. Involvement of the arms—particularly the extensor aspect of the elbows—was seen during 37 attacks. Much less frequently rash occurred on the face, mucous membranes, and trunk. A lesion not seen in any of the 52 cases from Taplow and Reading was perichondritis of one ear; it was, however, seen in three out of the 14 cases at the Postgraduate School. In one patient the ear was tender and red, and showed brawny oedema, the lesion

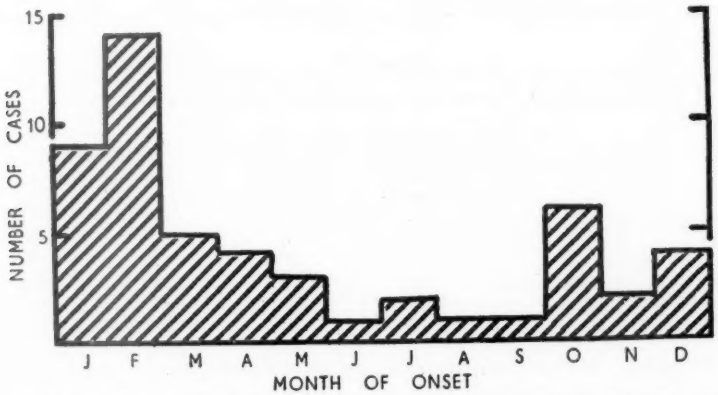

FIG. 2. Seasonal distribution of onset in 52 cases of Schönlein-Henoch purpura.

subsiding completely in a week. In the other two cases the lesion was more localized (Plate 20, Fig. 4), resembling a haemorrhagic blister at first, then becoming an indolent ulcer which, in a boy of five years, lasted five months.

Joints. Joint manifestations occurred in 38 attacks (67 per cent.), but were never followed by radiological or clinical residua. They were characterized by pain, limited movement, swelling, and occasionally effusion in the joints. The pain was frequently out of proportion to the physical signs. In contrast to rheumatic fever, migratory arthritis was infrequent; the more usual joint manifestations subsided with or without treatment in two or three days, rarely lasting longer than a week. The effect of treatment on arthritis was difficult to judge, as the symptoms and signs subsided so rapidly without it. Two patients, treated with aspirin and corticotrophin respectively, had a recurrence of arthritis during the treatment. The joints most frequently involved were the knees and ankles; less frequently the hips, wrists, and elbows were affected. Involvement of the small joints of the hands and feet was much less common. Effusion into the joints was usually slight, and in only one of the Taplow–Reading cases was examination of synovial fluid made. This showed a viscous fluid containing a moderate number of polymorphonuclear cells and a protein content of 2·7 gm. per 100 ml. In two of the Postgraduate School cases, however, fluid was aspirated from joints, and yielded 5 ml. and 8 ml. of sterile fluid from the knees of one patient, and 20 ml. from the other. The latter specimen showed 10,000 cells per c.mm. (62 per cent. polymorphs), a normal amount of

glucose, 3·6 gm. of protein per 100 ml., and a high relative viscosity of 157. In the former case the protein was 2·1 gm. and 3·5 gm. per 100 ml.

Abdominal manifestations. Colicky abdominal pain was present during 33 out of the 57 attacks, and not infrequently led to admission to the surgical wards. The pain was usually central, though sometimes in the right iliac fossa, and guarding of the abdominal musculature and central or lower abdominal tenderness were present in most cases, but the presence of purpura or other manifestations of the syndrome, together with the nature of the pain, usually led to the

TABLE II

Incidence of Manifestations of Schönlein-Henoch Purpura

	Canadian Red Cross Memorial Hospital	*Royal Berkshire Hospital*	*Total*	
			Number	%
Number of attacks	30	27	57	
Rash	30	26	56	98
Joint manifestations	22	16	38	67
Abdominal symptoms and signs	17	16	33	58
Renal involvement	13	10	23	40
Localized oedema	13	10	23	40

correct diagnosis. Melaena occurred during 10 of these attacks, and of the remainder the benzidine test for occult blood was positive in six of 10 patients tested. Four patients were subjected to laparotomy. One of these patients was found on two occasions to have ileocolic intussusception necessitating bowel resection. The findings at laparotomy in the other three were strikingly similar, and consisted of dilatation, thickening, and redness of the terminal ileum or jejunum, with haemorrhagic patches under the peritoneum over the adjacent bowel. A moderate amount of clear fluid was present in the peritoneum on one occasion, and enlarged mesenteric glands in all three cases. Laparotomy did not relieve colic, but no complications of operation were experienced. Since our analysis was completed another interesting case has been seen. During a relapsing course of over six months the patient showed all the manifestations of the syndrome, and he was subjected to laparotomy because of symptoms simulating appendicitis. At operation large mesenteric glands were found, and histological examination of one gland showed marked eosinophilic infiltration. The patient's white blood count at the time was normal, and has never shown eosinophilia.

Renal manifestations. Haematuria was found in 23 attacks in 20 patients; it was gross in 12 attacks, and microscopic only in 11. It was usually associated with proteinuria, but two patients had repeated attacks of marked haematuria without significant albuminuria or casts during a period of several months, both eventually making an apparently complete recovery; the follow-up period, however, is short, and the possibility of renal damage developing later is not excluded. Residual albuminuria, presumably indicating chronic nephritis, was seen in five children (10 per cent. of the series) at follow-up examination after complete subsidence of other signs (Table III), but in one of them it disappeared between six months and one year from the onset. In only one of the five was the

albuminuria gross in degree, and accompanied by mild hypertension (138/90) three years from the onset. One boy, aged eight years, who had moderate albuminuria, casts, and haematuria for seven weeks, developed massive haematuria, and died of uraemia three weeks later. At autopsy bilateral renal vein thrombosis was found, but no glomerular changes beyond what might be expected from this lesion. Generalized oedema was seen on five occasions, including this fatal case. In the other four children the oedema occurred in the

TABLE III

Renal Manifestations in Schönlein-Henoch Purpura

	Canadian Red Cross Memorial Hospital	*Royal Berkshire Hospital*	*Total*	*Number of patients*
Number of attacks	30	27	57	52
Haematuria:				
Frank	8	4	23	20 (38%)
Microscopic only	5	6		
Albuminuria	11	10	21	18 (35%)
Generalized oedema	2	3	5	5 (10%)
Hypertension	3	1	4	4 (8%)
Chronic nephritis	3	2	5	5 (10%)

Duration from onset to onset of renal abnormalities:

0–2 weeks	10 cases
2–4 weeks	5 „
4–6 weeks	4 „
Over 6 weeks	1 case

acute stage, and was mild and transient; two of these four developed residual albuminuria. Hypertension of a mild degree, for example 130/90, was seen transiently in the acute stage in the fatal case, and in two patients who had residual albuminuria (one of whom is mentioned above). Signs of renal involvement often appeared later in the course of the syndrome than other manifestations; in 25 per cent. of cases they were first found at periods greater than a month from the onset.

Localized oedema. Patches of localized oedema (in the absence of arthritis) are seldom seen in rheumatic fever but, in contrast, are frequent manifestations of Schönlein-Henoch purpura. Thus, of the 52 patients, they were seen in 23, 19 of whom had no evidence of renal involvement. The oedema was seen most commonly round the eyes, sometimes unilaterally (Plate 20, Fig. 5), or on the dorsum of the hands and feet, and sometimes occurred several times in the course of the attack. Less commonly patches occurred over the back and the genitalia; when appearing as the initial symptom, this feature caused considerable diagnostic discussion. The areas were poorly demarcated and not tender, and the oedema usually disappeared within two or three days. In five cases bruising became evident as the oedema subsided, but in the remainder there was no residuum. The protein-content of the oedema fluid was found to be high (5·6 gm. per 100 ml.) on the one occasion when sufficient fluid was obtained to make the estimation.

Other manifestations. One patient in the series had a well-documented history

of an attack of acute rheumatic fever two years before the onset of Schönlein-Henoch purpura, and had been left with an aortic diastolic murmur, which did not subsequently change. Two other patients during the course of the illness developed transient soft apical murmurs, one diastolic, the other mitral pansystolic. In all other respects these attacks were similar in severity, manifestations,

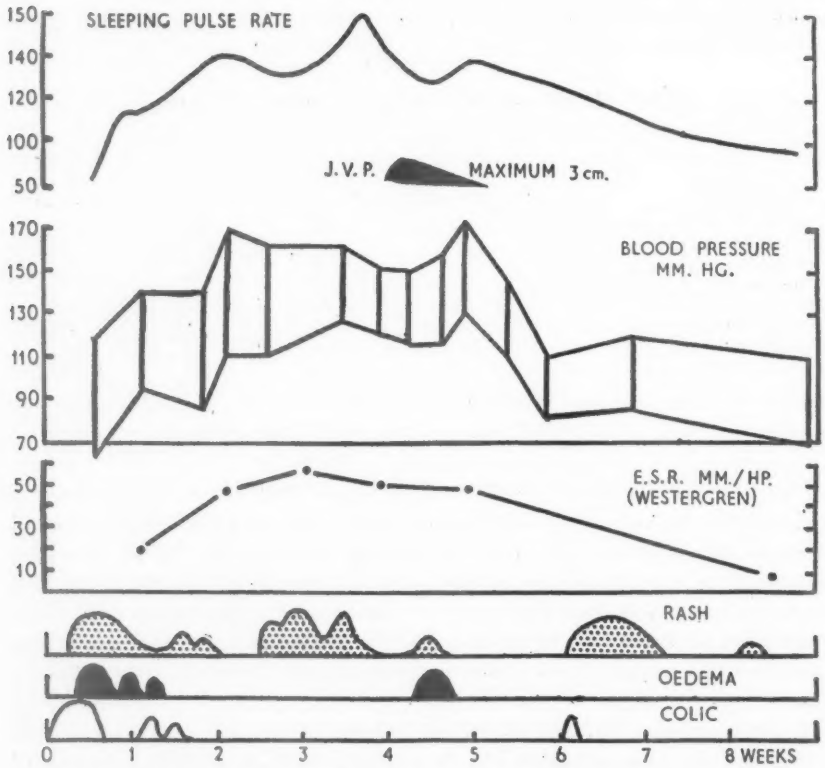

FIG. 3. Chart of a boy aged 12, showing a rise of blood-pressure during the active phase of purpura, without any urinary abnormality or increase of blood-urea. Follow-up examination four months from the onset showed no abnormality except a palpable spleen; there was no albuminuria.

J.V.P. = jugular venous pressure. E.S.R. = erythrocyte sedimentation rate (Westergren).

and duration to others in the series, and at follow-up examination no cardiological abnormality could be found. Other less common manifestations included intraocular haemorrhage (one case) and enlargement of the liver (four cases). Transient but severe hypertension was seen in a boy aged 12 at the Postgraduate School, in the absence of renal involvement and of nitrogen retention. It was accompanied by a raised jugular venous pressure, and flattening and inversion of the T wave in lead II at the height of the cardiac failure; earlier, nine days after his admission, the electrocardiogram had been normal. The course of his

illness was otherwise typical, and there were no residua at follow-up examination (Fig. 3).

Laboratory studies. The erythrocyte sedimentation rate was estimated during the active stage during all but four attacks. In the great majority of cases it was raised, usually to a moderate degree (Table IV), but in a few (13 per cent.) normal sedimentation was found (less than 15 mm. per hour (Wintrobe)). The Hess positive-pressure capillary fragility test was performed during the active stage in 18 cases, but gave a positive result in only four cases. Bleeding and

TABLE IV

Erythrocyte Sedimentation Rate (Wintrobe) during Active Schönlein-Henoch Purpura

	Canadian Red Cross Memorial Hospital	*Royal Berkshire Hospital*	*Total*	*% of known cases (53 attacks)*
Number of attacks . . .	30	27	57	..
Sedimentation rate:				
Not known . . .	1	3	4	..
0–14 mm./hr. . . .	5	2	7	13
15–19 „ . . .	1	5	6	11
20–39 „ . . .	14	5	19	36
40+ „ . . .	9	12	21	40

coagulation times were estimated in the majority of cases, and were always within normal limits, with platelet counts usually 150,000 or more per c.mm., though occasionally as low as 120,000 per c.mm. A slight polymorphonuclear leucocytosis was seen in about half the cases, while in the remainder both the total and differential counts were within the limits of normal. Rose tests and examination for L.E. cell factor were negative.

Histology. Gairdner (1948) remarked on the similarity of the histological appearances in his cases to those described in the case of erythema annulare published by Carol and van Krieken in 1935. A biopsy of the rash was therefore taken in six cases, and compared histologically with the rash of rheumatic fever (11 cases) and Still's disease (six cases) (Isdale and Bywaters, 1956). There was a close similarity between the rashes of rheumatic fever and Schönlein-Henoch purpura, except for the presence of extravasated red blood-cells in the latter. In both the major feature was perivascular accumulation of polymorphonuclear leucocytes and the products of nuclear breakdown, as well as occasionally a few eosinophils. This accumulation was often very dense (Plate 21, Fig. 6). In the later stages a few fragments of nuclear 'dust', an occasional polymorph, and unchanged erthrocytes were seen in the papillae and dermis. In none of these six biopsies, nor in three more taken from the Postgraduate School series of patients, was fibrinoid necrosis of the skin vessels seen, but in one of the latter series, a woman of 45 who subsequently died of uraemia with hypertension and was examined *post mortem*, fibrinoid necrosis was seen in the small vessels of the periadrenal fat (Plate 21, Fig. 7). There were, in addition, subacute glomerulonephritis with gross crescent formation, small foci of necrosis in the myocardium,

and a small focus of fibrinoid change in the anterior cusp of the mitral valve. A subcutaneous nodule taken for biopsy from the elbow of this patient showed 'collagen necrosis', and will be more fully described elsewhere (unpublished data). It seems possible that the arteriolar fibrinoid necrosis may have been closely related to the acute hypertension, since in other cases in which similar changes, with myocardial necrosis, have been found, acute hypertension has been a salient factor (Levitt and Burbank, 1953, Case V; Lecutier, 1952).

Onset and course. Upper respiratory-tract infection had preceded the majority of the attacks, the characteristic manifestations usually following within two weeks. The first sign was most frequently rash, either alone (18 cases) or in conjunction with other manifestations (15 cases). Less often joint manifestations were the first feature (nine cases, and 12 in which involvement of joints and other signs occurred together). Colicky abdominal pain was the first symptom in 11 cases, and oedema (usually with purpura) in five. Renal signs tended to occur later, and only in two children, who had had previous attacks with nephritis, were such signs present at the onset, or within two days of it. The duration of the attack varied from a week to several months. When there was no evidence of renal involvement the majority of attacks (28 out of 32, or 87 per cent.) lasted less than six weeks; the attacks lasted longer than six weeks in more than 60 per cent. of the patients who had nephritis. About 10 per cent. of the cases ran a relapsing course, with fresh crops of rash, localized oedema, haematuria, and (less often) arthritis.

Effects of treatment. Three patients were given antihistamine drugs in adequate dosage; no improvement resulted, and all three showed fresh manifestations of the disorder during treatment. Salicylate was not used unless there was arthritic pain; in the few cases in which it was so employed assessment was difficult, but the drug did not appear to be very efficacious. Cortisone up to 150 mg. per day, or corticotrophin in equivalent dosage, was administered to eight patients in the Royal Berkshire Hospital. In a few cases the treatment appeared to be of benefit and was followed by improvement, but in five cases fresh manifestations occurred during the treatment. One patient with rash and nephritis appeared to improve with cortisone, and to relapse when it was discontinued, subsequently improving again on its resumption. Soon after the second course, however, there was a further recurrence, and, although cortisone was not given for this relapse, recovery ensued, apparently complete and as rapid as in the previous episodes. In a few cases which had run a protracted course tonsillectomy appeared to be of benefit, although it sometimes produced a temporary exacerbation of rash or haematuria.

Prognosis. In cases without nephritis there was rapid and complete recovery. In about 10 per cent. of cases there was persistent proteinuria and haematuria. The one death resulted from renal vein thrombosis. Two other serious complications were seen in one girl; she had two attacks of intussusception, both requiring bowel resection, with a 10-week interval between them, and also had haemorrhage into the iris and vitreous of one eye, leading to blindness. She

subsequently developed chronic nephritis with sustained proteinuria and haematuria.

Pathogenesis

In no instance among the 52 patients could any food antigen be incriminated, and on the four occasions when drugs, particularly sulphonamides, were suspect, later administration of a careful provocative dose failed to produce any symptoms. One child had asthma before, during, and after treatment, and one had had infantile eczema. In 41 of the 57 attacks the illness was preceded within

TABLE V

Upper Respiratory-Tract Infection

			Antistreptolysin O titre			*Group A β-haemolytic streptococci (during first week)*		
	Number of cases	*Upper respiratory-tract infection*	*Raised (200 or over)*	*Not estimated*	*Normal (< 200)*	*Recovered*	*Not sought*	*Not found*
Canadian Red Cross Memorial Hospital:								
1st attack	28	23	7	3	18	6	5	17
2nd attack	2	1	1	..	1	(1*)	..	1
Royal Berkshire Hospital:								
1st attack	24	14	..	24	..	1	18	5
2nd attack	2	2	..	2	..	..	2	..
3rd attack	1	1	..	1	..	..	1	..
Total (number of attacks)	57	41	8	30	19	8	26	23
Percentage of those tested	..	72%	30%	..	..	26%	..	..

* β-haemolytic streptococcus not grouped.

four weeks by an infection of the upper respiratory tract, either tonsillitis (including two cases of scarlatina) or, less frequently, acute otitis media. The usual duration of the infection before the onset of purpura or other manifestations was two weeks or less, with a median duration of one week.

Group A β-haemolytic streptococci were recovered from nose, throat, or ear swabs on seven out of 30 cases (23 per cent.) within a week of entry to hospital (Table V). Those organisms which were successfully typed belonged to types 1, 6, 12 (two patients), and 22. Only one of those successfully typed (one of the two type 12 infections) was associated with the finding of albumin and red blood-cells in the urine. In the other two cases scarlatina preceded the onset of symptoms by two to three weeks, and in one of them the antistreptolysin O titre (A.S.O.) was estimated and was found to be raised. A.S.O. titres were estimated in the first week, and usually at weekly intervals during the first month of admission, in 27 out of 57 attacks. An A.S.O. titre above 200 was

reported in six cases (range 500–2,500), including three of the seven patients in whom group A β-haemolytic streptococci were isolated, and also one of the scarlatina cases. In a majority of the cases A.S.O. titrations were repeated: in only one of the patients with an initially normal titre (1:125) did the figure rise by one tube to 200 during the first month. One other patient yielded an initial titre of 200, which rose no further. This figure is often considered the upper limit of normal. Correlation of an A.S.O. titre of 200 or more and the finding of group A β-haemolytic streptococci was poor. Organisms of this group were isolated from four patients with a raised A.S.O. titre, and from three with normal titres. Taking either an A.S.O. titre above 200, or isolation of the organism in the first week, as a 'positive' result, only 11 out of 33 attacks in which one or both tests were applied, and only 10 out of 25 in which both were applied, gave a positive result. Experience at the Postgraduate School with a group including rather more adult patients (seven out of 13 over the age of 12) showed a somewhat higher proportion of patients (four out of 10) to have an A.S.O. titre above 200 (none with nephritis) in the first week after admission, but group A β-haemolytic streptococci were not recovered in the three cases investigated. Two other patients had a titre of 1:200; in three other cases without raised A.S.O. titres haemolytic streptococci were isolated, but organisms of group A were found in only one of these three cases, and appeared in only one out of five swabs in the first week. There was no correlation with age, all adult patients at Taplow, and two out of five in the Postgraduate School series, yielding normal A.S.O. titres. Thus evidence of infection with group A β-haemolytic streptococci sufficient to cause a rise in the A.S.O. titre above 200 occurred in six out of 27 attacks (22 per cent.), or 10 out of 37 (27 per cent.) if the Postgraduate Medical School cases are added.

To establish the significance of these results, patients who were seen within a month of onset of the first attack of the syndrome have been compared with patients suffering from acute rheumatic fever seen in their first attack within a month of its onset,[2] and with other patients admitted to hospital with a non-rheumatic diagnosis. No satisfactory series of normal children seen in hospital is available: the present control group of children in hospital were suffering from a variety of non-rheumatic illnesses, ranging from osteomyelitis to leukaemia. The children in the three groups were all under the age of 12 years, and in every case culture of throat swabs for streptococci, A.S.O. titre estimations, and an inquiry into the presence or absence of preceding upper respiratory-tract infection were made. Nineteen of the 52 children with purpura satisfy these criteria, and are compared in Table VI with the group of 107 children with rheumatic fever and the 40 in whom a non-rheumatic diagnosis was made. A significantly greater proportion of the children with Schönlein-Henoch purpura

[2] Except for one nine-month period, consistent results have been found in the cases of rheumatic fever in the hospital. To establish A.S.O. figures for acute rheumatic fever in children under 12, patients admitted during this nine-month period were excluded. A more detailed analysis of the A.S.O. titres in these children is reported elsewhere (Holborow and Isdale, 1956). During this period of unreliable A.S.O. estimations it happened that no patient with Schönlein-Henoch purpura was admitted.

had a history of upper respiratory-tract infection, as compared not only with the non-rheumatic group ($\chi^2 = 18{\cdot}24$; $P < 0{\cdot}001$), but also with the rheumatic fever group ($\chi^2 = 9{\cdot}3$; $P < 0{\cdot}01$). The incidence of recovery of group A β-haemolytic streptococci in the purpura group was intermediate between that found in the rheumatic fever group and that found in the non-rheumatic group, but not significantly different from either. In contrast, the incidence of raised

TABLE VI

Comparison of Rheumatic Fever, Control, and Schönlein-Henoch Purpura Cases in Children under 12 Years Old

	Non-rheumatic (control) group (NR)	*Schönlein-Henoch purpura* (SHP)	*Acute rheumatic fever* (RF)	*Significant difference*
Number of cases . .	40	19	107	..
Incidence of raised A.S.O. titre (1:200 or more) .	13 (32%)	7 (35%)	81 (76%)	RF/others: $\chi^2 = 11{\cdot}56$; $P < 0{\cdot}001$
Mean A.S.O. titre (geometric)	71	130	288	..
Incidence of upper respiratory tract infection .	12 (30%)	17 (89%)	56 (52%)	SHP/RF: $\chi^2 = 9{\cdot}3$; $P < 0{\cdot}01$ SHP/NR: $\chi^2 = 18{\cdot}24$; $P < 0{\cdot}001$
Recovery of group A β-haemolytic streptococci .	5 (12%)	5 (26%)	47 (44%)	No significance

A.S.O. titres was comparable in the purpura and non-rheumatic groups, and significantly greater in the rheumatic fever group than in the others ($\chi^2 = 11{\cdot}56$; $P < 0{\cdot}001$). The geometric mean of the actual A.S.O. levels was significantly higher in the rheumatic fever group than either of the other groups. The mean A.S.O. titre in the purpura group was higher than in the non-rheumatic group, but the difference is not significant.

Discussion

In his original paper Schönlein (1837) noted the frequency with which infection of the respiratory tract preceded the onset of peliosis rheumatica, and later authors have stressed this association. The haemolytic streptococcus was emphasized by Gairdner (1948) as an important aetiological factor, because this organism was recovered from the throat in many of his cases, either during the active stage or later, with or without a clinical tonsillar infection; Gairdner, however, made no comparison with other children; no evidence of a raised titre of streptococcal antibody was furnished, and no grouping of organisms was done. Similarly Derham and Rogerson (1952) found haemolytic streptococci in 15 out of 21 cases, but the organisms were typed in only three cases (types 6, 12, and 15). Kreidberg, Dameshek, and Latorraca (1955) found β-haemolytic streptococci in only one out of 15 cases, all of which were preceded by an upper respiratory infection. The finding in the present survey that 72 per cent. of attacks were preceded by infection of the upper respiratory tract conforms with

Gairdner's experience, but, as regards the incidence of recovery of group A β-haemolytic streptococci, this group of cases is intermediate between the rheumatic fever and control groups studied in hospital. In contrast, neither the incidence of raised antistreptolysin O titres nor the mean antistreptolysin O titre differed significantly in the control and Schönlein-Henoch purpura groups, but both were significantly higher in the acute rheumatic fever group. Ten of

TABLE VII

Antistreptolysin O Response in relation to Age

	Non-rheumatic group			*Schönlein-Henoch purpura*			*Acute rheumatic fever*		
Age (years)	*Number of cases*	*A.S.O. titre 200 or over*	*Mean A.S.O. titre*	*Number of cases*	*A.S.O. titre 200 or over*	*Mean A.S.O. titre*	*Number of cases*	*A.S.O. titre 200 or over*	*Mean A.S.O. titre*
0–5	13	2	49	6	2	112	20	9	144
6–9	14	5	93	9	3	89	55	45	318
10–11	13	6	87	4	2	174	32	27	380
Total	40	13	71	19	7	130	107	81	288

the 28 patients with Schönlein-Henoch purpura at the Canadian Red Cross Memorial Hospital had been given chemotherapy or penicillin lozenges for a few days, before admission within two weeks of the onset of the upper respiratory-tract infection; but three of these 10 patients showed a rise in antistreptolysin O titre, and it is not thought that preceding treatment had effectively altered the antibody response or the recovery of group A β-haemolytic streptococci.

In an analysis of the rheumatic fever group (Holborow and Isdale, 1956) it was found that the antistreptolysin response varied with age. It is well established that young children show a diminished response to uncomplicated streptococcal infection (Rantz, Maroney, and Di Caprio, 1951); but, contrary to Coburn and Pauli's claim (1935), we found the diminution of antistreptolysin response in younger children to be of the same degree in rheumatic fever as in the absence of rheumatism. The group of cases of Schönlein-Henoch purpura included a high proportion of young children, and a comparison of antistreptolysin responses has therefore been related to age in Table VII. The numbers of cases are small, but there seems to be less variation with age than in the two non-purpuric groups. It is clear that further elucidation of this apparent paradox is needed. Alternative possibilities are that the organisms produce only weak streptolysin antigen, or that the patients fail to develop adequate antibodies thereto. It would be of interest to measure other antibody responses.

Conclusion

Although, therefore, Schönlein-Henoch purpura starts in most cases within one or two weeks of an upper respiratory infection, this infection is due to group A β-haemolytic streptococci in only about one-third of the cases; in such cases this finding may be a chance occurrence, since a similar incidence of raised antistreptolysin O titres was seen in a control group of non-rheumatic children in hospital. An alternative possibility (if the syndrome is one of the sequelae of group A β-haemolytic streptococcal infection) is that the formation of antistreptolysin O antibody is sometimes defective. Further elucidation of this point is needed; it would be interesting to know what other streptococcal antigens, for example fibrinolysin, evoke a response in such cases.

Summary

Data regarding 64 cases of Schönlein-Henoch purpura, collected from three centres, are reviewed in the light of the hypothesis of a group A β-haemolytic streptococcal aetiology. Serum antistreptolysin O titres were found to be raised in one-third of the cases, an incidence equal to that found in a control series of non-rheumatic children, and half of that seen in children with rheumatic fever, admitted to hospital. Group A β-haemolytic streptococci were isolated in one-quarter of the cases investigated; this incidence was intermediate between that found in rheumatic fever and that found in a control series of children admitted for non-rheumatic conditions. Thus, though there are close clinical and pathological similarities between this condition and rheumatic fever and nephritis, there is no clear evidence, as there is in the two latter diseases, of infection with group A β-haemolytic streptococci as an invariable causative factor.

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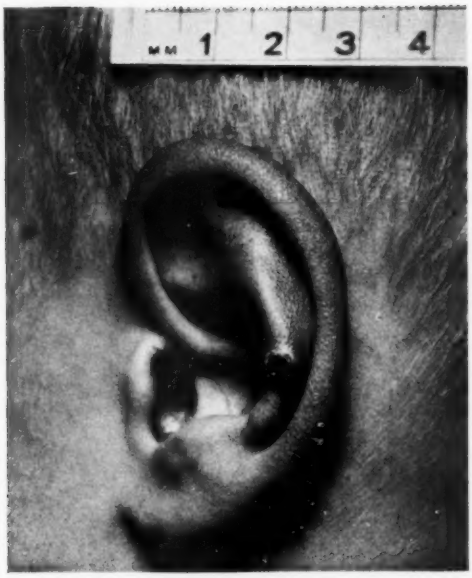

FIG. 4. The ear of a boy aged five, showing superficial ulcerated lesions

FIG. 5. Unilateral swelling of the forehead and orbital region in a boy aged five

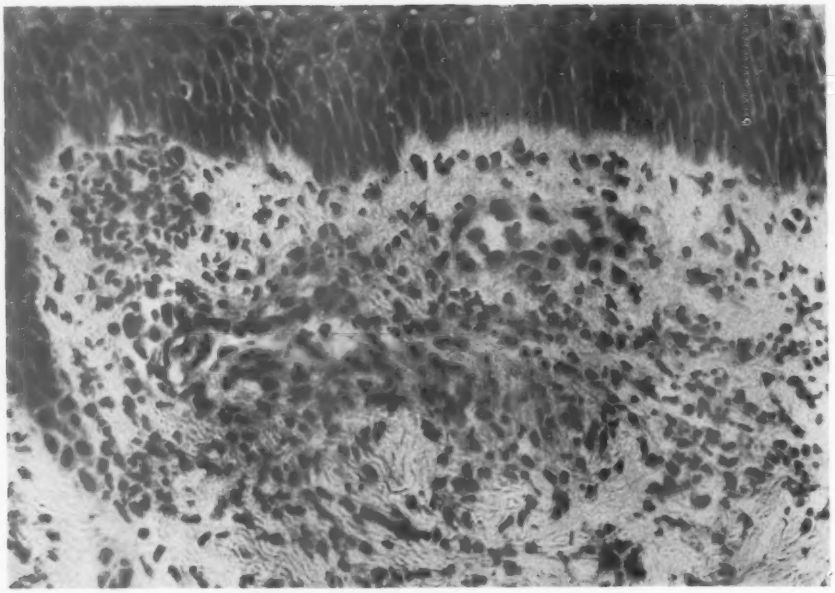

FIG. 6. Microscopic appearance of skin (haematoxylin and eosin, × 235) in a girl aged six years with Schönlein-Henoch purpura, showing extravasated red cells, polymorphs, and perivascular polymorph debris

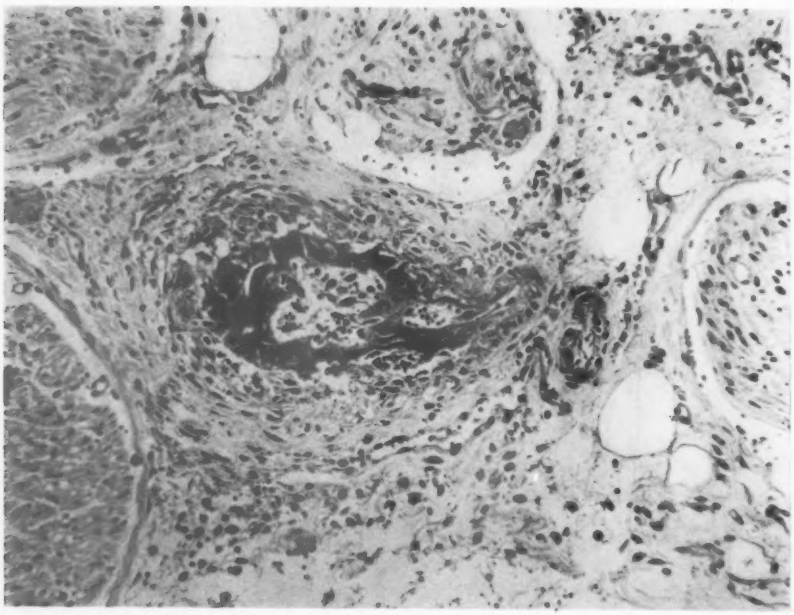

FIG. 7. A small artery from the periadrenal fat in a woman aged 45, who subsequently died of uraemia, showing fibrinoid necrosis (haematoxylin and eosin, × 165)

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SOME ASPECTS OF CERVICAL SPONDYLOSIS[1]

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This paper is based on the clinical study of 78 patients with cervical spondylosis and a neurological deficit; its purpose is to present information related to the diagnostic problems encountered, the significance of antecedent trauma, and the effects of medical and surgical treatment, and, in the light of certain findings at operation, to discuss in brief the pathogenesis of the myelopathy which was associated with the spondylosis.

Schmorl (1929) first drew attention to the importance of the intervertebral disks in health and disease by his autopsy studies. His work, together with that of Andrae (1929) and others from the Dresden school, was summarized in the English language by Beadle (1931). They have shown that the intervertebral disk spaces may be narrowed either as a sequel to herniation of the nucleus pulposus or by dessication and degeneration consequent upon age. Whichever process occurred the result was the same, namely circumferential osteophytosis of the vertebral rims and osteoarthropathy of the neuro-central joints, with or without partial vertebral subluxation. Such changes, which have come to be described by the term 'spondylosis', may be sufficiently pronounced to cause encroachment on the root-exit foramina or narrowing of the spinal canal. Though a number of clinical publications antedated this appreciation of the underlying lesions, the first comprehensive account of the neurological complications of cervical spondylosis was given by Stookey (1928), who described the syndromes arising from 'univentral' and 'biventral' compression of the spinal cord and of the cervical nerve-roots. At the time he considered the causative lesion to be a chondromatous tumour, and the same error was made by Elsberg (1928, 1931) who found that 'chondromata' formed 17 per cent. of the extradural spinal tumours. Peet and Echols (1934) showed that these 'chondromata' were in fact calcified intervertebral disk protrusions. Since then much has been written about the clinical aspects of cervical spondylosis, and we are especially indebted to Brain (1948, 1954 *a*, *b*) for most of the information we possess today. In spite of the volume of the work, which has been reviewed by Frykholm (1951) and by Brain, Northfield, and Wilkinson (1952), there remain certain lacunae in our knowledge, which it is the aim of the present paper to fill. Their nature has already been indicated, and the literature relevant to these special aspects of cervical spondylosis will be reviewed in the appropriate sections.

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Patients Investigated and Methods

The diagnostic criteria for inclusion of patients in the present series were as follows: (1) A history and physical signs compatible with a myelopathy, a cervical radiculopathy, or both. (2) Evidence of spondylosis on the plain radiographs of the cervical spine. (3) The finding at myelography of anterior indentation of the myodil column, beyond the normal range, opposite one or more cervical intervertebral disk spaces. Seventy-seven patients fulfilled these requirements; one other, in whom a myelogram was not done, but confirmation of the cervical spondylosis was obtained at laminectomy, is included. Sixty-one patients were admitted to the Departments of Neurology or Neurosurgery at the General Infirmary, Leeds, between the years 1952 and 1956 inclusive. The remainder were admitted to the Departments of Neurosurgery at the Radcliffe Infirmary, Oxford (13), and the General Hospital, Newcastle upon Tyne (four). Seventy-three patients were seen personally on one or more occasions; in five cases details were obtained entirely from the clinical records supplemented by postal information. In addition to the routine general and neurological histories, information was sought regarding the patients' past and present occupation, and in particular whether their employment involved the maintenance of abnormal postures of the neck or necessitated either forced or repeated movements of the cervical spine. If one or more of these factors had operated for eight or more years it was considered that the patient had been subjected to 'occupational stress'.

Physical examination of the general and neurological systems was conducted on the orthodox lines but, when gait was defective, the extent of this disablement was numbered according to the following scale:

Grade 1. No abnormality of gait noticeable to the examiner, but activity stated to be less than normal.
Grade 2. A noticeable abnormality of gait, but ability to walk not less than half a mile without assistance.
Grade 3. Walking without assistance limited to less than half a mile.
Grade 4. Ability to walk up to half a mile with the aid of one stick.
Grade 5. Ability to walk up to 300 yards with the aid of one stick.
Grade 6. Ability to walk up to 300 yards with the aid of two sticks.
Grade 7. Ability to walk only with support or with elbow crutches.
Grade 8. Inability to stand unsupported.

The initial grade of walking was measured personally in 45 patients; in 11 it was estimated from the clinical records in conjunction with postal information, and in three by subsequent interview. The same designation was used in all later observations to assess the results of treatment.

All patients were submitted to lumbar puncture, and the results of the spinal manometric observations were obtained from the clinical records. These indicated that the procedure had been carried out with the neck in flexion and extension in 60 cases; in the remainder there was no mention of the posture of the neck. Anteroposterior, lateral, and oblique radiographs of the cervical spine were taken in 72 patients; in six no oblique radiographs were taken. Seventy-seven patients were submitted to myodil myelography, six by the cisternal and 71 by the lumbar route. All the plain radiographs, and 70 of the 78 series of radiographs taken at the time of myelography, were examined by the author. The presence or absence of a myelographic spinal block was added from the radiologist's report.

By surgical treatment is here understood cervical laminectomy, sited before operation by myelography, the details of which are included in the appropriate

section. Three of the operations were attended by the author; in 28 cases details were obtained from the surgeon and the clinical records. Twenty-six of the patients treated by surgery wore a polythene or leather collar for two months after operation. By medical treatment is understood immobilization of the neck in a polythene collar. When myelopathy was present, the minimum period of such treatment was three months; when there was evidence of cervical radiculopathy alone, it was six weeks. Collars were worn day and night by 33 patients; for eight a modified collar made of rubber or paper was provided for night wear, as they were unable to tolerate one made of polythene. Additional treatment included the administration of hypnotics until patients had become accustomed to sleeping in collars, and mephenesin carbamate, in oral doses of up to 3 gm. eight-hourly, when spasticity was marked or flexor spasms troublesome. All patients with a significant disorder of gait were admitted to a rehabilitation unit for exercise therapy and, when necessary, the provision of walking appliances. Follow-up observation was conducted wholly in person in 55 patients, by a combination of personal examination and perusal of the case records in 15, and in five, treated by surgery, entirely from the case notes and postal information.

In a study of occupational stress, patients of either sex between the ages of 46 and 65 admitted to a general medical ward, and without spontaneous neurological complaint, were questioned about their past and present occupations. These patients were divided into three groups: (1) Those who had sustained occupational stress for eight or more years. (2) Those who neither had sustained occupational stress nor recalled a significant injury to the head or spine. (3) A group in which the question of trauma remained in doubt. Group 3 was discarded. Patients in Groups 1 and 2 were questioned for symptoms referable to the nervous system or neck, and were examined, and a single lateral radiograph was taken of the cervical spine. Twenty-five patients in each group were accepted without further selection.

The term 'neuronopathy' is used to describe a neurological deficit attributable to a myelopathy, a neuropathy, or both.

Initial Clinical Features

The diagnosis of neuronopathy due to cervical spondylosis in six patients was shown by events within the subsequent three years to be incorrect, and these patients will be described in a later section. The remaining 72 fell into two clinical groups: (1) Those with a myelopathy, with or without a cervical radiculopathy (55). (2) Those with a cervical radiculopathy, without evidence of myelopathy (17).

Age and sex distribution. Table I shows that the age at onset was 39 to 66 years in Group 1, and 28 to 66 years in Group 2. The younger patients in both groups were men, and the average age at onset was five to 10 years later in women. Table II shows the ratio of men to women, which was in the region of 4:1.

Mode of onset. The duration of symptoms prior to examination was from three months to nine years, and averaged 2·3 years. Almost all patients gave a history of steady deterioration, though in five it was spontaneously arrested for periods of one to three years, and one patient had a remission. The rate at which the syndrome evolved varied, so that there was no definite correlation

between duration of symptoms and extent of disablement. Six modes of onset were recognized: (1) Symptoms due to involvement of cervical nerve-roots, either sensory or motor, or both (18 cases). (2) A similar onset, later giving rise to a progressive paraplegia (19 cases). (3) More rarely, symptoms were referred to the upper and lower limbs simultaneously (five cases). (4) Symptoms due to a progressive paraplegia with little or no sensory disturbance and, after intervals

TABLES I AND II

(Group 1, myelopathy; Group 2, radiculopathy only.)

I. *Age at Onset*

		Group 1	*Group 2*	*Groups 1, 2*
Average age at onset:	Men	47	50	47
	Women	56	57	56
	Both sexes	48	51	49
Age limits:	Men	39–66	28–66	28–66
	Women	46–65	50–63	46–65
	Both sexes	39–66	28–66	28–66

II. *Sex Distribution*

	Men	*Women*	*Total*
Group 1	42	13	55
Group 2	15	2	17
Groups 1, 2	57	15	72

of months or years, involvement of the upper limbs (14 cases). (5) Symptoms and signs restricted to the lower limbs throughout the period of observation (nine cases). (6) An atypical group of eight cases, of which three presented tingling in the feet, two sciatica, but with evidence of a myelopathy, one angina pectoris, and one girdle pain. The first three modes of onset indicated a lesion of the cervical cord or nerve roots, but the remainder suggested localization to the dorsi-lumbar cord or the cauda equina.

Symptoms

Neck stiffness and pain. Rather more than one-third of the patients experienced aching pain in the posterior cervical region, often radiating to the scapular region, and accompanied by stiffness and limitation of movement. The greater number of these patients also complained of brachialgia.

Brachialgia. Twenty-five patients had pain in the upper limbs; three varieties were recognized: (1) Intermittent 'stabbing' pain which passed centrifugally in the pre- or post-axial border of the limb, to reach the elbow (three), the wrist (four), or the digits (10 cases). It was often made worse by coughing, straining, and movements of the neck, usually those of rotation and lateral flexion to the contralateral side, less often by such movement to the ipsilateral side or by extension. (2) Persistent dull and often 'burning' pain, imperfectly localized to the forearm (three), the wrists and palms (two), or the thenar eminence (two cases). It was not influenced by straining or by movements of the neck. (3) Intermittent 'stabbing' pain which passed centripetally from the wrist to the elbow when the ipsilateral shoulder was abducted (one case).

Pain elsewhere. One patient complained of retrosternal pain which, during periods of exertion, became severe and radiated down the left arm; the heart

was normal on electrical and clinical examination. A further nine had sciatica at some time during the period of observation, and eight experienced a 'burning' and poorly localized pain in the lower limbs.

Other sensory symptoms. Rather more than half the patients (41) complained of paraesthesiae. In 29 a sensation of numbness or tingling involved one or more of the digits, together with a greater or lesser portion of the palm and

TABLE III

The Disability in Walking before Treatment

Number of patients		*Grade of disability of gait*
Medical	*Surgical*	
12	3	None
1	2	1
3	0	2
11	1	3
6	4	4
2	7	5
5	6	6
1	5	7
0	3	8
41	31	

forearm; in 12 other patients complex subjective disturbances of sensation, often of a thermal quality, were referred to the thighs, calves, or feet.

Motor symptoms. A slight clumsiness or weakness of the hands was not uncommon (32 cases), though seldom troublesome, and this contrasted with the considerable stiffness of the legs of which the greater number of patients in Group 1 complained; six of the latter also had flexor spasms. The degree of impairment of walking, in patients selected for medical and surgical treatment respectively, is shown in Table III.

Disorders of sphincter control. Twenty-three patients in Group 1 had a disturbance of sphincter control: in 20 it did not amount to more than a slight hesitancy or precipitancy of micturition; in two patients there was incontinence of both urine and faeces, and one had retention of urine which necessitated catheterization. These symptoms were invariably associated with considerable spasticity of the lower limbs and extensor plantar responses.

Physical signs

Cranial nerves. Signs referable to the cranial nerves were detected in 10 patients, and included nystagmus (five cases), which was rhythmic and within the limits of binocular vision, Horner's syndrome (four), and exaggeration of the jaw-jerk (two cases).

Signs referable to the neck. Painful limitation of neck movement (15 cases) was most often associated with signs of a cervical radiculopathy; rotation and lateral flexion to the contralateral side—less often to the ipsilateral side, or extension—were chiefly affected. When brachialgia was present these manœuvres aggravated the pain. Painless restriction of neck movement was more

common (25), and was not especially associated with brachialgia. With the exception of flexion, which was usually normal, all excursions were restricted to about equal extent. One patient experienced paraesthesiae, which passed from the cervical region into the digits of all four extremities, when he flexed his neck, and another complained of tingling in the hypochondrium and thighs which was provoked by the same action—a well-known sign seen in many forms of cervical myelopathy.

Signs referable to the motor system. Muscular wasting involved the upper limbs in 29 cases—slight in 17, moderate in seven, and severe in five. The intrinsic muscles of the hand, with or without the adjacent forearm, were affected in 17 cases, and in the remainder the musculature of the shoulder girdle. Fasciculation, present in 12 cases, was usually confined to the territory of wasted muscles and inconspicuous, but in three patients it was prominent and diffuse over the upper limbs and pectoral region. In the upper limbs, spasticity (21 cases) rarely amounted to more than a catch of resistance in the supinators of the forearm, and was often accompanied by some clumsiness of fine finger movement and relative weakness of the abductors and extensors of the fingers. In 23 cases weakness was detected within the territory of a spinal segment. The great majority of patients in Group 1 had a disturbance of gait, due to a combination of spasticity and weakness, and sometimes also to sensory loss; the grade of disability is shown in Table III. The striking feature was the predominance of spasticity over weakness, and 25 patients exhibited sustained ankle and patellar clonus.

The deep tendon-reflexes. All patients in Group 1 had extensor plantar responses, with exaggeration of the knee- and ankle-jerks, and in about half of them the abdominal responses were absent. In over two-thirds of all cases the state of the upper-limb reflexes did not help to localize the lesion to the cervical cord; for they were normal in 25 and uniformly increased in 25. In 22 cases, however, the abnormalities which were found indicated a focal lesion between the fifth and seventh cervical segments: these signs included inversion of the supinator reflex, with diminution or absence of the biceps- and exaggeration of the triceps-jerks (five), the absence of one or more reflexes (15), and the exaggeration of one or two reflexes, the remainder being normal (two cases).

Signs referable to the sensory system. Cutaneous sensory loss of three types affected 43 patients: (1) An area composed of lower cervical and upper dorsal dermatomes, over which pain, temperature, and to a lesser extent touch, were impaired (four cases). The relative sparing of touch and the 'suspended' character of the deficit suggested an intramedullary lesion of the cervico-dorsal cord, such as syringomyelia. (2) An area composed of peripheral portions of dermatomes between C6 and D1 inclusive, over which all modalities of sensation were impaired, though the findings were often minimal (23 cases). (3) An area characteristic of involvement of the long sensory tracts, with a fairly well defined upper level (27 cases).

In eight patients the upper extent of the deficit was below the knee; in 13 it was between D10 and D3; in six it was continuous with sensory loss in the

territory of cervical dermatomes. In three patients there was a partial Brown–Séquard syndrome, with loss of pain and temperature sense on one side and impairment of vibration and joint-position appreciation on the other. All modalities were usually affected, though to different degrees, and sparing of sacral segments was not found. In 19 patients vibration sense was lost below and including the pelvis and position sense was defective at the great toes. In 18 patients who had no cutaneous sensory loss, either vibration or postural sense, or both, were found to be impaired in the great toes.

The cerebrospinal fluid

One patient, who died, was found to have an intrathecal neurofibroma of the dorsal region in addition to cervical spondylosis; the results of analysis of his lumbar spinal fluid have therefore been discarded. Of the 71 that remain the spinal manometric observations were normal in 61, in eight indicated a partial block, and in two a complete block. In 22 patients the lumbar cerebrospinal-fluid protein was increased to between 56 and 200 mg. per 100 ml. This number included 14 in whom there was neither manometric nor myelographic evidence of a spinal block, and in these patients the protein levels were between 56 and 120 mg. per 100 ml. (average 96 mg.). It was of interest that two patients had evidence of a partial block with a chemically normal cerebrospinal fluid.

Radiography

Plain radiographs. Fifty-nine patients were found to have loss of the cervical lordosis, generalized in 42 and focal in 17 cases. A slight degree of vertebral subluxation was present in six patients. One or more of the cervical disk spaces were narrowed in 68 patients, this finding being single in 28, double in 26, triple in nine, and quadruple in five cases. In 11 of the 14 cases in which three or more disk spaces were involved, calcification was shown by linear streaks within the disk substance. Anterior and posterior osteophytosis of the vertebral rims was seen in every patient; it tended to be greatest when adjacent to a narrowed disk, and more extensive anteriorly than posteriorly. There was no correlation between the size of the posterior osteophytes and the severity of the neurological deficit. Oblique radiographs, which were taken in 64 cases, showed moderate to marked encroachment on the intervertebral foramina in 37, limited to a single foramen in 18, in 14 involving two, and in five three or more foramina. Once again there was often little correlation between the clinical and radiological findings, for almost complete occlusion of a foramen occurred without clinical evidence of radiculopathy, and such evidence was sometimes found without radiological change at the appropriate foramen. Congenital anomalies were found in four patients, and included fusion of the pedicles of three vertebrae, fusion of the bodies of two or of three vertebrae, and spina bifida occulta. In both types of vertebral fusion the severest spondylotic change was found adjacent to the anomaly.

Myelography. All the 77 patients submitted to myelography showed anterior indentation of the myodil column in the cervical region. In three the filling defect appeared to be opposite the body of a vertebra rather than a disk space. In the remainder the indentations were adjacent to one or more disk spaces,

and the frequency with which the various levels were involved is shown in Table IV. Thirty patients showed a single indentation, 24 showed two, 12 showed three, and five showed four indentations. These abnormalities were not found opposite the first disk space, and were opposite C7–D1 in only two cases. Over 90 per cent. of the lesions occurred between C4 and C7, with a maximum incidence at C5–6. In addition to these findings four patients were found to have a

TABLE IV

The Level of the Myelographic Abnormality

Level of indentation of myodil column	*Number of patients*
C2–3	0
C3–4	18
C4–5	32
C5–6	47
C6–7	34
C7–D1	2

posterior filling defect at the same level, which at first sight suggested an extramedullary spinal tumour. In general there was correlation between plain radiographs and myelography as regards the situation of the lesion, though occasionally myelographic indentations occurred opposite a disk space which appeared to be normal on the plain films, while the finding of gross spondylosis in such radiographs was not invariably accompanied by a myelographic abnormality at the same level. It was also noticed that the extent of the neurological deficit bore little relation to the magnitude of the myelographic abnormality, though, as will be shown, patients with multiple indentations tended to deteriorate in spite of medical treatment. In the anteroposterior radiographs it was often possible to determine transverse bars of increased translucency which corresponded in site to the indentations seen in the lateral films. These were not unequivocal findings, and some difficulty was experienced in distinguishing the appearances from the normal. Attempts to study the dural root-pouches also proved disappointing; for a site showing apparent abnormality on one occasion was not infrequently later found to be normal. It is possible that air myelography would have been a more rewarding method of studying the root-pouches. In three patients the central ribbon of relative translucency, due to the position of the spinal cord, appeared to be widened over one or two segments, a finding which at first sight suggested an intramedullary tumour. Lateral views of the same region showed this appearance to be caused by slight dorsal displacement of the cord by a disk protrusion. A further three patients were found to have a complete spinal block, and 12 to have a partial block; they included 10 patients with a spinal manometric abnormality, and five others.

An important point is that no feature was identified, in the myelograms or plain radiographs, by which it was possible to distinguish the six cases of neuronopathy due to a different lesion from those due to cervical spondylosis.

Diagnostic Problems Related to Cervical Spondylosis

The problems are of two kinds: first, the features of the neuronopathy attributable to this condition may resemble those of other disease; second, the finding of radiological spondylosis and a neurological deficit affords no assurance that the former gives rise to the latter.

The earlier accounts by Stookey (1928), Dandy (1929), and Mixter and Ayer (1935), indicated that the progressive myelopathy of cervical spondylosis was often difficult to distinguish from spinal tumour, while, if cutaneous sensory loss was present, the upward extent of the deficit within dorsal segments of the spinal cord might result in faulty localization of the lesion. Further, analysis of the lumbar cerebrospinal fluid at times revealed an increase of protein (Stone, Arieff, Kaplan, and Brown, 1941; Semmes and Murphey, 1943; Broager, 1944; Kahn, 1947), though it remained doubtful whether this increase occurred only in association with a spinal block; for, as Kaplan and Kennedy (1950) have shown, the spinal manometric observations must be made with the neck flexed and extended before concluding that they are normal, and few have observed these conditions. In the present series, however, protein levels of up to 120 mg. per 100 ml. occurred without either manometric or myelographic evidence of a block. Most often these diagnostic problems are resolved by myelography, but Trowbridge and French (1954) have described artefacts which gave the appearance of tumours. It has been seen that a spinal tumour may be suggested by the site of the indentation being adjacent to a vertebral body rather than a disk space. This appearance is probably related to a previous soft nuclear herniation which has been displaced caudally to this site by the posterior common ligament. In addition, a posterior filling defect, not unlike that produced by a spinal meningioma, was found in four patients, and in three of these who came to operation the evidence indicated that it was caused by thickening of the ligamentum flavum. Somewhat similar findings have been described by Taylor (1953). Lastly, the ribbon of relative translucency attributable to the position of the spinal cord may be broadened, so that it resembles in appearance an intramedullary tumour.

When sensory symptoms and signs are inconspicuous or absent, a neuronopathy due to cervical spondylosis may be mistaken for motor-neurone disease (Bucy, Heimburger, and Oberhill, 1948; Strully, Gross, Schwartzman, and von Storch, 1951; Liversedge, Hutchinson, and Lyons, 1953). The following example illustrates the nature of the problem.

Case 1. A man aged 60 had noticed progressive wasting and weakness of the left hand for five years before admission to hospital. After two years he was unable to extend the fingers, and noticed involuntary twitching of the muscles of the chest wall and arms. Examination revealed no abnormality of the cranial nerves. Fasciculation was seen over the left upper limb and pectoral region, and there was moderate global wasting and gross weakness of the left hand and forearm. The motor system was otherwise normal, and no sensory loss was detected. The deep tendon-reflexes were not remarkable apart from the left supinator and biceps jerks, which were diminished, and the left triceps jerk, which was increased; the abdominal reflexes were preserved, and the plantars flexor. Plain radiographs of the cervical spine showed loss of the normal lordosis,

and narrowing of the disk spaces at C4–5, 5–6, and 6–7 with considerable anterior and posterior osteophytosis of the adjacent vertebrae. There was marked encroachment on the intervertebral foramina at the same levels on the left side. A myelogram revealed indentation of the myodil column opposite the disk spaces C5–6 and 6–7. The pressure, manometrics, and constituents of the lumbar cerebrospinal fluid were not remarkable. A diagnosis was made of neuronopathy due to cervical spondylosis, and the patient was treated with a polythene collar for six months. A follow-up for two years showed no evidence of deterioration. The prominent and diffuse fasciculation, and the absence of sensory deficit, at first suggested a diagnosis of progressive muscular atrophy, but the state of the tendon-reflexes indicated a focal lesion rather than a system disease.

The importance of an abnormality of the upper limb reflexes in this connexion has been stressed by Spillane and Lloyd (1952) and Brain (1954*a*). It should also be noted that a long duration of symptoms may not by itself exclude motor neurone disease, for Müller (1952) has suggested that such patients may live for 30 years.

When disseminated sclerosis arises in middle age the clinical course is often a slow progression, without the remissions and relapses exhibited by younger patients (Brain, 1936). It is not remarkable, therefore, that the distinction from cervical spondylosis should often be difficult. Moreover, Strully, Gross, Schwartzman, and von Storch (1951) have described spontaneous remissions in patients with a myelopathy due to cervical spondylosis. One patient in the present series reported a spontaneous remission, but he was not examined during this phase. Lastly, the finding of nystagmus in five patients suggested at first a lesion within the posterior cranial fossa and, in view of the other physical signs, disseminated sclerosis.

Den Hartog Jager and Moffie (1949) and Brain, Northfield, and Wilkinson (1952) have emphasized the necessity of excluding subacute combined degeneration of the spinal cord in patients who present a progressive paraplegia. The following case report illustrates a problem related to this disease.

Case 2. A man aged 45 developed progressive weakness and stiffness of the left leg four years before admission to hospital, and two years later the right leg was similarly affected. At about this time he complained of intense paraesthesiae of the digits of both hands. On examination there was considerable spastic weakness of both lower limbs, with sustained ankle and patellar clonus. The deep tendon-reflexes were normal in the upper limbs, and increased in the lower; the abdominal reflexes were absent, and the plantar responses extensor. Vibration sense was absent below the 12th dorsal spine, and position sense was absent in the toes and reduced at the ankles. There was relative hypalgesia and hypaesthesia below the 10th dorsal segments. A blood count revealed a macrocytic anaemia (2,900,000 red cells per c. mm.; haemoglobin 65 per cent.). There was histamine-fast achlorhydria, and examination of the bone-marrow established the diagnosis of pernicious anaemia. Treatment with vitamin B_{12} was instituted, 100 μg. by intramuscular injection, at first twice a week, and later once a fortnight. The peripheral blood picture was normal at the end of six months, but his walking had deteriorated. Plain radiographs of the cervical spine showed narrowing of the disk space at C4–5, and vertebral osteophytosis at C4–5, 5–6, and 6–7. A myelogram revealed indentations of the myodil column at these levels. All the evidence supported the diagnosis of myelopathy

attributable to cervical spondylosis, and he was treated with a polythene collar. After 18 months his condition was found to be unchanged.

The possibility of the concurrence of pernicious anaemia and cervical spondylosis during or after middle age makes it necessary to carry out full investigation of patients with paraplegia, and to include myelography. Neglect to do so in this patient led to a diagnostic error.

Less often the neuronopathy of cervical spondylosis may mimic syringomyelia. Oppenheimer (1938) described 14 patients with unilateral oedema, cyanosis, wasting, and loss of reflexes, restricted to the upper limb, and associated with encroachment on the ipsilateral intervertebral foramina by osteophytes. Müller (1950–1) described patients with dissociated sensory loss attributable to cervical spondylosis, and in four cases in the present series the character and distribution of the sensory deficit suggested syringomyelia, though in all other features, including the age of onset, the absence of body asymmetry or skeletal deformity, and the presence of the upper limb reflexes, there was little resemblance. Since the publications of Hanflig (1936), Turner and Oppenheimer (1936), Mettier and Capp (1941), and McKenzie and Botterell (1942), cervical spondylosis has been incriminated with increasing frequency as a cause of brachialgia. Elliott and Kremer (1945) and Lund (1945) each described eight patients with root pain in an upper limb, which was attributed to cervical spondylosis. Frykholm (1951) has shown how various syndromes once attributed to 'neuritis', cervical rib, and thoracic inlet abnormalities, have come to be recognized as radiculopathy due to cervical spondylosis. Nevertheless, as has been shown, there is often lack of correlation between the site of the foramen occluded by osteophytes and the nerve-root which is involved. Frykholm (1951) has demonstrated that cervical spondylosis often gives rise to root-sleeve fibrosis with compression radiculopathy, without much encroachment on the foramina. Occasionally the pain due to root compression by osteophytes or root-sleeve fibrosis may mimic coronary ischaemia (Nachlas, 1934; Hanflig, 1936; Semmes and Murphey, 1943). Pain of this character was a feature in one case in the present series. Knight (1948) has shown that such pseudo-angina may occur when the seventh cervical nerve-root is compressed. Frykholm (1951) has reminded us that the radiation of root pain is not confined to the dermatome, but may extend throughout the sclerotome. This accounts for the frequent complaint of upper back and shoulder pain and to pseudo-angina in patients with cervical spondylosis. Barré (1926) and Lieou (1928) described a bizarre syndrome in patients with 'arthritis of the neck' which included vertigo, headache, vasomotor disturbances, and facial pain. The existence of this syndrome is open to doubt, but Ryan and Cope (1955) have reported vertigo in association with cervical spondylosis. They attributed the vertigo to a disorder of the tonic neck-reflexes, since it proved possible to provoke both vertigo and nystagmus by movements of the neck irrespective of the position of the head in space. Another unusual symptom of cervical spondylosis is dysphagia, which was reported by Bauer (1953). No examples of these rarities have been encountered in the present series.

The second diagnostic problem, namely whether a neuronopathy can be attributed to radiologically determined cervical spondylosis, has received scant attention in the literature. Pallis, Jones, and Spillane (1954) reported that half of the subjects, in a sample of hospital patients over the age of 50 without any neurological complaint, had cervical spondylosis determined by plain radiographs, and of these subjects about half had unsuspected signs indicative of a

TABLE V

The Percentage of New Patients diagnosed as having Myelopathy due to Cervical Spondylosis, Disseminated Sclerosis, and Parkinsonism

Diagnosis	*1951*	*1952*	*1953*	*1954*	*1955*
Myelopathy attributed to cervical spondylosis	..	0·4	1·4	1·6	2·3
Disseminated sclerosis	5·4	4·2	3·0	3·6	2·7
All types of Parkinsonism	2·4	2·2	1·9	2·2	2·2

myelopathy or a neuropathy, or both. This is in agreement with the autopsy studies of Horwitz (1940) and Morton (1950), both of whom reported an incidence of about 75 per cent. in patients over the age of 50. In view of this frequency it must be expected that cervical spondylosis will be fortuitously associated with other causes of neuronopathy. There has always been a number of patients with paraplegia of uncertain origin and, with each advance in our knowledge of the pathology of the spinal cord, there has been a tendency to attach to these the latest diagnostic label. There is little doubt that today this label is cervical spondylosis. In this hospital there has been a steady increase in the use of this term to explain myelopathy, and with it a reluctance to make a diagnosis of disseminated slcerosis, to a point at which, as Table V shows, the incidence of the two conditions appears to be the same. Marshall (1955) followed up 52 patients at one time diagnosed as having paraplegia of undetermined cause, and examined the autopsy records in a further 32 similar cases. It was possible in only six to incriminate disease of the intervertebral disks and, in the autopsy series, a well defined pathological explanation of the neurological deficit was found in each case. The most common cause was disseminated sclerosis, which was detected in two-thirds of the cases that came to autopsy.

In the present series 61 patients were admitted to the General Infirmary at Leeds, and in six cases subsequent events indicated that a disease other than cervical spondylosis was responsible for the neuronopathy. It will be recalled that there were no clinical or myelographic features to distinguish this group from the remainder. Of the examples which follow, the first case illustrates the difficulty in the distinction from disseminated sclerosis.

Case 3. A woman aged 52 developed stiffness of both thighs, and a feeling of numbness of the left leg, in June 1948. In March 1950 she complained of tingling of the finger-tips, and her walking began to deteriorate. She was admitted to hospital in April 1954. On examination the cranial nerves and upper limbs were normal. There was a moderate spasticity and weakness of the lower limbs, with sustained ankle and patellar clonus. The left triceps-jerk and both knee- and ankle-jerks were increased, the abdominal reflexes were absent, and the

plantar responses were extensor. Vibration sense was absent below the pelvis, the threshold for position sense was increased in the great toes, and there was relative hypalgesia below the level of D6 on either side. Radiographs of the cervical spine showed narrowing of the disk spaces at C5–6 and 6–7, and considerable osteophytosis of the adjacent vertebral rims. The lumbar spinal-fluid pressure, manometrics, and constituents were normal, and a myelogram revealed anterior indentation of the myodil column at C5. A diagnosis was made of myelopathy attributable to cervical spondylosis, and the patient was treated with a polythene collar. There was no improvement, and in May 1955 she developed a transient squint with diplopia, and her gait became unsteady. She was readmitted to hospital in June 1955, when examination revealed bitemporal pallor of the optic disks, rhythmic horizontal nystagmus, cerebellar ataxia of all four limbs, and a spastic paraplegia. There was impairment of vibration and postural sense in both lower limbs, but no impairment of cutaneous pain sense was detected. Analysis of the lumbar spinal fluid showed protein 50 mg. per 100 ml., and a Lange curve 5543210000. All the evidence now suggested disseminated sclerosis, and that the radiological detection of spondylosis in the neck was irrelevant.

The second example of an erroneous diagnosis follows. In this case it is probable that part of the syndrome was due to cervical spondylosis, but the main disability to a different cause.

Case 4. A woman aged 57 fell in 1949 and dislocated her left shoulder. Thereafter she complained of increasingly severe attacks of stiffness and pain in the neck, and after two years the pain radiated down the pre-axial border of the left upper limb to the wrist. There was no change in her condition until April 1953, when she developed progressive wasting and weakness of the left hand. She was admitted to hospital in April 1955. Examination revealed a painless restriction of all cervical movements except flexion. Fasciculation was seen in the left pectoral and scapular regions, and in the left forearm. There was a moderate global wasting of the left forearm and hand, with proportionate weakness. There was no dystonia or sensory loss, and the right upper and both lower limbs were normal. The biceps-jerks were both diminished, the remainder of the reflexes increased, the abdominal reflexes absent, and the plantar responses extensor. The lumbar spinal-fluid pressure, manometrics, and constituents were normal. Plain radiographs of the cervical spine showed narrowing of the disk spaces at C5–6 and 6–7, with anterior and posterior osteophytosis of the adjacent vertebrae and marked encroachment on the lower intervertebral foramina. A myelogram showed indentation of the myodil column opposite the disk spaces C5–6 and 6–7. A diagnosis was made of radiculopathy and myelopathy attributable to cervical spondylosis, and the patient was treated with a polythene collar. Her condition continued to deteriorate, and she was readmitted to hospital in September 1955. Examination revealed a marked slurring dysarthria, dysphagia, a brisk jaw-jerk, bilateral facial weakness, and fasciculation and wasting of the tongue. There was widespread fasciculation over the upper limbs and trunk. Global wasting affected both forearms and hands, especially the left. Tone was slightly increased in all four limbs. All the evidence now suggested motor neurone disease, though it is probable that the stiffness and pain in the neck and the brachialgia were due to cervical spondylosis.

Two patients, whose condition was at first attributed to cervical spondylosis, were found later to have cerebral degeneration. In one there was no gross mental

change, and when he died as the result of a pulmonary infection the autopsy finding was unexpected. The presence of cervical spondylosis was confirmed, but there was no abnormality of the cervical cord. It is probable that the spasticity and weakness of the lower limbs was due to the cerebral disease. A description of the second patient follows.

Case 5. A woman aged 61 had never been 'much of a scholar', and had left school at the age of 13, two standards below the top. Two years before admission to hospital she had developed a progressive weakness and stiffness of the lower limbs. On examination she was a woman of modest intelligence, but with a fairly good grasp of current events, and fully orientated in time and space. Speech was normal, and the cranial nerves were intact. There was a catch of spasticity in both forearms, and moderate spasticity of the lower limbs, with sustained ankle and patellar clonus. Fine finger and toe movements were clumsy, but otherwise power was preserved, and sensation intact. All the deep tendon-reflexes were increased, the abdominal reflexes absent, and the plantar responses extensor. The blood-pressure was 150/80. Plain radiographs of the skull and chest were normal, as were the pressure, manometrics, and constituents of the lumbar spinal fluid. Plain radiographs of the cervical spine showed narrowing of the disk spaces at C4–5 and 5–6, with osteophytosis of the adjacent vertebral bodies. A myelogram revealed indentation of the myodil column opposite the disk spaces C4–5 and 5–6. A diagnosis was made of mental backwardness, with myelopathy attributable to cervical spondylosis. During the following year her husband reported evidence of mental deterioration, and she was readmitted to hospital. She was found to have a profound dementia, and to be disorientated in time and space. The remainder of the physical signs had not altered. A lumbar air encephalogram showed uniform enlargement of the cerebral ventricular system and pooling of the air over the occipital and frontal poles. All the evidence now pointed to a cerebral degeneration, and it is probable that the neurological signs were attributable to the same cause.

These two patients recall those described by Lhermitte (1907), in whom spastic paraplegia preceded dementia by a period of years. The diagnostic error in the case which follows would, in all likelihood, not have been exposed but for the patient's death.

Case 6. A man aged 50 began in July 1950 to complain of burning pain, increased by exercise, in the region of both ankles and knees. In November 1951 he experienced weakness and stiffness of the legs; this progressed over a period of eight months. In July 1952 he developed hesitancy of micturition, and intermittent pain in the left elbow and the base of the left thumb, and in November 1952 he was admitted to hospital. There was moderate weakness and spasticity of the lower limbs, with sustained ankle clonus. The deep tendon-reflexes were normal in the upper limbs and increased in the lower limbs, and the plantar responses were extensor. The upper abdominal responses were preserved, but the lower were absent. Vibration sense was absent below and including the pelvis, and position sense was defective in the toes of both feet. Plain radiographs of the cervical spine showed loss of the lordosis, narrowing of the disk space at C5–6, and anterior and posterior osteophyte formation from the adjacent vertebral bodies. The lumbar spinal-fluid pressure and manometrics were normal, and the fluid contained no cells and 56 mg. of protein per 100 ml. A myelogram revealed indentation of the myodil column opposite the disk space C6–7. A diagnosis was made of myelopathy attributable to cervical spondylosis. On November 20, 1952 Mr. W. H. Henderson performed a laminectomy

from C3 to D1. The dura was widely opened, and no displacement of the neural contents of the meningeal envelope was seen. There was a hard transverse bar opposite the C6–7 disk space, about 1 cm. in width and 4 mm. in depth. Three dentate ligaments on either side were divided opposite this abnormality, but nothing further was done. The patient's condition remained satisfactory until midnight, when he was last seen; an hour later he was found dead.

At autopsy there was pulmonary oedema which was sufficient to have caused death. Examination of the spinal column confirmed the observation of a bony bar at the C6–7 disk space. The spinal cord was softened in the region of the sixth cervical segment, and there was a leash of thin-walled blood-vessels on the dorsal aspect, extending from D2 to the conus. Microscopy revealed a large haemorrhage in the anterior horn of the spinal cord at the level of C6 on the left, and a smaller one on the right. Wallerian degeneration extended from the second dorsal to the second cervical segments, involving the posterior columns. Below this level the appearances of the spinal cord were characteristic of an intramedullary racemose venous angioma.

The mistaken diagnoses in the five cases described above were all related to cervical spondylosis as a cause of myelopathy. In a sixth patient the diagnosis was concerned with a peripheral neuropathy.

Case 7. A woman aged 53 complained of numbness and tingling of all the finger-tips of both hands in May 1954; this symptom gradually extended to include the forearms. One month after the onset she noticed weakness of the hands, and began to experience attacks of nocturnal pain, lasting for two to three hours, involving the radial digits on either side. She was admitted to hospital in July 1954. She was found to have weakness of the right deltoid, of the extensors of the wrists and fingers, and of the intrinsic muscles of both hands. Two-point discrimination was impaired over the tips of the radial three digits on both sides. No other abnormality was detected. Plain radiographs of the cervical spine showed narrowing of the disk space at C6–7, and osteophytosis of the adjacent vertebral bodies. There was not much encroachment on the intervertebral foramina. The lumbar spinal-fluid pressure, manometrics, and constituents were normal, as were radiographs of the chest and both wrists. A myelogram revealed indentation of the myodil column opposite the disk spaces C3–4, C4–5, and C6–7. A diagnosis was made of radiculopathy attributable to cervical spondylosis, and she was treated with a collar. She was readmitted to hospital in August 1954, since there had been no improvement. A radiograph of the right shoulder showed osteoarthropathy which, it was considered, explained the weakness of the deltoid on that side. It was also thought that much of the weakness of the hands was due to pain which accompanied the exertion of full power. On August 13, 1954 Mr. J. M. P. Clark explored both carpal tunnels; the findings on each side were identical. Proximal to the transverse carpal ligament the median nerve was swollen, and it was flattened where it passed deep to the ligament. Division of the ligament showed that there was a palpable groove on the volar surface of the median nerve corresponding to, and probably caused by, the transverse carpal ligament. After operation the patient made an uninterrupted recovery, and had been free of symptoms for nine months when she was last seen. All the evidence in this case pointed to compression of the median nerves as the cause of the symptoms and signs. An erroneous diagnosis was suggested by the distribution of the weakness, which was beyond the territory of the median nerve, but in retrospect was explained by pain and osteoarthropathy of the right shoulder.

Thus, in six of 61 patients, subsequent events indicated that the cause of neuronopathy was other than the cervical spondylosis which was demonstrated to be present both by plain radiographs and by myelography. It is difficult to escape from the conclusion that among the remainder there are other cases of a similar kind.

The Significance of Trauma

Direct trauma. O'Connell (1955) has rightly drawn a distinction between soft herniations of the nucleus pulposus, which are usually single, and the multiple osteophytic bars due to degenerative disease. For a comprehensive study of the role of antecedent trauma in cervical spondylosis it is necessary to consider both these conditions. It has long been recognized that an injury to the neck, in the absence of fracture or dislocation, may give rise to a neuronopathy (Walshe and Ross, 1936; Broager, 1944; Walshe, 1944; Barnes, 1948; and others). It has been possible in most cases of this kind to incriminate a traumatic herniation of the nucleus pulposus in the cervical region. Barnes (1948) and Taylor and Blackwood (1948) described another mechanism, in which rupture of the anterior longitudinal ligament during hyperextension of the neck had permitted narrowing of the spinal canal and damage to the cord, and Taylor (1951) reported laceration of the spinal cord by forward protrusion of the ligamentum flavum. But these mechanisms are rare, and in the majority of cases the onset of a neuronopathy after injury to the cervical spine is related to changes in the intervertebral disks. O'Connell (1955) has indicated that in patients with nuclear herniations, if operation is long deferred, subsequent radiography reveals circumferential osteophytosis of the two adjacent vertebrae. Indeed, Keyes and Compere (1932) were able to provoke a focal spondylosis in dogs by inducing a traumatic nuclear herniation; and Milward and Grout (1936) watched the development of such spondylosis in patients who complained of low back pain after lumbar puncture; all the evidence suggested that the spinal puncture had provoked a nuclear herniation which was followed by the development of focal spondylosis. In the present series 10 patients were found to have spondylosis which was strictly limited to a single disk space and the two adjacent vertebrae, as determined by both plain radiographs and myelography. Five of them recalled an injury to the neck, and five had sustained repeated minor injuries likely to have affected the cervical spine. It seemed probable that this 'focal spondylosis' arose as the result of a nuclear herniation provoked by trauma. Further, observations during operation have indicated that all stages exist between the soft nuclear herniation and the osteophytic bar. Thus, three patients were found to have protrusions composed partly of bone and partly of softer tissue, and the consistency of the latter varied from that of cheese to that of finger-nail parings. The evolution was shown in another patient, who had a soft herniation at one level and an osteophytic bar at the adjacent disk space. The interval between injury and the onset of a neuronopathy, which is often a matter of years (Brain, Northfield, and Wilkinson, 1952), may represent

the time taken for the development of focal spondylosis. In the present series 16 patients recalled an injury which was considered to have been significant. In six of them neurological symptoms ensued with a matter of weeks, and in two within three months, of the accident. In the remainder the time intervals were between six months and 19 years; four patients in this group had stiffness and pain in the neck, and one had brachialgia, for a few days immediately after the injury. This incidence of 22 per cent. is in broad agreement with 16 per cent. given by Ricard and Masson (1951), though Brain, Northfield, and Wilkinson (1952) obtained a history of antecedent trauma in 36 per cent. of their series, while Semmes and Murphey (1954) considered the incidence to be insignificant.

Another important aspect was mentioned by Knight (1948), who showed that in elderly persons a relatively trivial injury might give rise to a profound neurological disablement. Symonds (1953) described the sudden onset of neuronopathy in patients with pre-existing cervical spondylosis, after incidental manipulations of the neck during tonsillectomy and dental extraction. He emphasized the dangers attendant on passive movement of the cervical spine when affected by spondylosis, especially under general anaesthesia. Two patients of the present series, who had been able to walk fairly well with the aid of one stick, and who had shown no evidence of deterioration for six and 18 months, sustained falls of a trivial character. In each there was an immediate access of gross neurological disability, and neither was able to walk again. It might be supposed that the cause was traumatic herniation of the nucleus pulposus from a cervical disk already the site of degenerative change, but a second myelogram did not support this contention.

Occupational stress. The probability that occupational stress, which has been defined in a previous section, is related to cervical spondylosis, is suggested by the predominance of male patients in this and other series, the earlier age of onset in men, and the site most often affected by spondylotic change (C5–6), the region which contributes most to the range of flexion and extension of the neck. Kellgren and Lawrence (1952), however, found no significant predisposition to the condition in coal-miners, though Miller (1956) showed that 90 per cent. of miners between the ages of 50 and 55 were affected, and in housewives the incidence was only about half this figure. In the present series 60 per cent. of the patients had been subjected to occupational stress, and when those who had sustained a significant injury are added the overall incidence of trauma, in the widest sense of the term, is 70 per cent. There was no great difference in this respect between the two clinical groups.

The selection of 25 patients who had neither complained of neurological symptoms nor been subjected to occupational stress has already been described, as well as that of a control group who, though they had sustained occupational stress, made no spontaneous complaint of such symptoms. The findings related to the plain radiographs of the cervical spine, which are summarized in Table VI, show that there was no significant difference between them in the frequency of spondylosis. Clinical assessment of these occupational groups showed,

however, that of the patients subjected to stress, eight complained of aching neck pain, three had brachialgia, and one experienced paraesthesiae in the index finger on one side; in the stress-free group three complained of aching neck pain and one of brachialgia. Examination showed that 10 patients in the first group had signs of a myelopathy or cervical radiculopathy, while in the second group only one was affected. The neurological signs here included are

TABLE VI

The Incidence of Cervical Spondylosis in Patients without Neurological Complaint, in relation to Occupational Stress

	Normal	*Slight spondylosis*	*Moderate spondylosis*	*Marked spondylosis*
25 patients subjected to occupational stress	5	3	6	11
25 patients free from occupational stress	6	4	7	8

wasting of the intrinsic muscles of a hand with relative weakness, extensor plantar responses, loss or inversion of the upper-limb reflexes, and sensory loss within the territory of a cervical dermatome. Minor differences in the deep tendon-reflexes, or in the appreciation of vibration, have been excluded as equivocal. The evidence suggests that occupational stress does not materially influence the development of cervical spondylosis but, in the presence of this condition, predisposes to neurological complications, which are often asymptomatic.

Congenital malformations. A third aspect of trauma is related to congenital anomalies of the cervical spine, which by their nature cause limitation of movement at one or more intervertebral disk spaces. McKenzie and Botterell (1942) and Collins (1949) have shown that these anomalies give rise to an excess of movement at the adjacent disk spaces to compensate for the segmental restriction of mobility, and at these sites spondylotic change is especially prone to develop. Three examples of this nature have already been described.

Treatment

There is no intention of comparing the results of surgical and medical treatment, for, as will be shown, the selection of patients for operation meant that the most seriously disabled were submitted to surgery and the least affected were treated by medical means.

Medical Treatment

The treatment of radicular syndromes was originally derived from that given to patients with acute nuclear herniations. Nachlas (1934) used a modified Thomas collar, and reported improvement of brachialgia. Others, including Hanflig (1936), Turner and Oppenheimer (1936), and Mettier and Capp (1941), preferred intermittent cervical traction, carried out either manually or by means of a block and tackle. Philip (1950), who also employed neck traction, pointed

out that without any treatment a remission usually occurred. Cyriax (1954) demonstrated that during traction the cervical disk spaces may be widened to twice their normal thickness, and later (1955) stated that 90 per cent. of patients with neck pain or brachialgia obtained relief after manipulation of the neck. Most neurologists have been impressed with the dangers of such treatment when the intervertebral disks are 'brittle', though there is little doubt that it is usually most successful.

The medical treatment of myelopathy attributable to cervical spondylosis is relatively modern; indeed, as recently as 1948 Brain recommended surgery for all cases with evidence of compression of the spinal cord. Later, however, the dangers of cervical laminectomy were appreciated, and Spicer and Bayless (1949) recommended immobilization of the neck by means of a special brace. Spillane and Lloyd (1951) used a polythene collar for the same purpose, and this has become the mainstay of modern treatment. It is surprising that, in spite of the widespread use of this appliance, little has been written concerning the effects of treatment. One of the few published references to it is by Brain, Northfield, and Wilkinson (1952). Of the 10 patients treated two died and two could not be traced, four were improved, and two showed no change. The authors concluded that patients over the age of 50 or with a long history, and those with arterial hypertension or atheroma, were best treated medically, owing to the poor results of surgery. Brain (1952) has suggested that a period of neck traction is often beneficial before the wearing of a collar, but Liversedge, Hutchinson, and Lyons (1953) considered that traction was helpful only in the treatment of root pain.

Results of medical treatment

The disturbance of gait. Gait was abnormal in 29 patients, and the severity of the disorder is shown in Table III. Subsequent progress was related to the nature of the myelographic abnormality. When there was evidence of a single major indentation, with or without a second minor one, the condition is described as focal spondylosis; when the findings indicated two or more major indentations the condition is described as generalized spondylosis. In the latter group it will be recalled that there was often calcification within the disk substance. Fig. 1 shows the results of the follow-up in the 29 patients as regards the state of walking. At the end of two months examination showed little change: 10 patients were slightly improved, 16 unchanged, and three worse. Twenty-nine were followed up for one year: two had died, one from an acute pulmonary infection and the other from bronchial carcinoma, and one was untraced. Of the 26 examined nine were improved, 11 were unchanged, and six had deteriorated; in general the degree of improvement or of deterioration had increased. This trend was yet more apparent at the end of two years, when 12 were improved, six were unchanged, and eight had deteriorated. A closer analysis shows that the condition of patients with focal spondylosis had remained static or was better, except in one patient who had shown initial improvement but had exhibited an access of disability after a fall. The extent of

the improvement was between one and two grades, and 14 patients were able to lead useful lives. By contrast, the patients with generalized spondylosis did badly: only one made a transient improvement, while the remainder either deteriorated or showed no change. Of the original 14 patients with generalized spondylosis, after two years one was dead, one was untraced, seven were worse, and four unchanged. The extent of the deterioration was considerable, for four

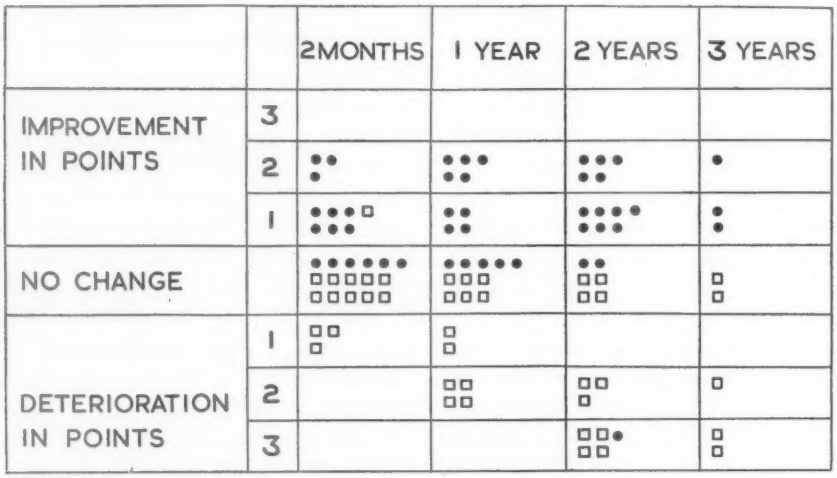

FIG. 1. Scatter diagram showing the results of the follow-up, as determined by the state of walking, in 29 patients treated with polythene cervical collars.
Squares signify patients with generalized spondylosis; dots signify those with focal spondylosis.

were able to walk less than 300 yards with the aid of sticks, and three a similar distance with one stick. Deterioration was not related to age, the initial grade of disablement, or the duration of symptoms, though the amount of improvement was less marked in patients with long histories or with much initial disability.

Root pain. Two of the 13 patients with brachialgia obtained no relief from medical treatment; in both the character of the pain was dull and 'burning', and poorly located to the wrists and palms. The pain was ameliorated in all the other patients within a matter of days of assuming their collars, and complete relief was obtained in from seven days to three months. Two relapsed within six and 18 months respectively, but were relieved by a further period of immobilization of the neck.

Impairment of sphincter control. Slight hesitancy or precipitancy of micturition was present in six cases, and in five normal sphincter control was restored within three months; in one patient the abnormality persisted throughout the two-year period of observation.

Sensory symptoms and signs. Twelve patients complained of tingling of the finger-tips; this symptom resolved in five patients, was improved in six, and

persisted unchanged in one. Cutaneous sensory loss within the territory of cervical dermatomes was not affected by treatment, but of nine patients who had hypalgesia and hypaesthesia over the lower limbs or trunk, in six both the density of the decifit lessened and the level receded; in three the defect remained unaltered.

Other observations. Three of the patients with signs of a myelopathy became normal. In those of the remainder who showed improvement in walking, spasticity of the lower limbs became less and power improved. No measurements, however, were attempted, and the lessening of the signs was not more than a clinical impression.

In summary, patients with generalized spondylosis did badly as judged by the state of their walking and, though a few did not deteriorate, the majority were left with serious disablement. By contrast, those with focal spondylosis did fairly well, and three with a moderate initial disability became normal. Sensory symptoms and signs tended to be refractory to treatment, apart from brachialgia, which usually resolved within a matter of weeks when a collar was worn.

Surgical Treatment

The earlier accounts of the treatment of cervical spondylosis were given exclusively by surgeons, since the distinction from spinal tumour was infrequently made before operation. Stookey (1928) recommended laminectomy, opening of the meningeal envelope, and attempted removal of osteophytic bars, which necessitated division of dentate ligaments. Hawk (1936) described 17 patients treated by surgery, adding one patient of his own. Stookey (1940) in an appraisal of operative treatment, concluded that the results were far less favourable than those obtained in comparable cases of spinal tumour, the difference being probably due to the technical difficulties of removing a hard mass anterior to the spinal cord. By contrast, Love and Camp (1937), Love and Walsh (1938), Semmes and Murphey (1954), and O'Connell (1955) have indicated that removal of soft nuclear herniations in the cervical region is usually followed by a large measure of improvement. Though radical surgery occasionally obtained good results, most neurosurgeons became familiar with the great dangers attendant upon attempted removal of osteophytes protruding from the anterior wall of the spinal canal, and had occasion to meet patients rendered quadriplegic by this procedure. Thus most of the recent reports have related to a limited decompression by laminectomy and division of dentate ligaments opposite the lesion. Ricard and Masson (1951) described 24 patients treated in this way, with a mortality of 12 per cent.; the immediate results were satisfactory, but only 14 were followed up for one year: three had died, two had continued to improve, seven remained unchanged, and two, who had shown initial improvement, had later deteriorated. Brain, Northfield, and Wilkinson (1952) described 21 patients, of whom 19 survived operation; later observation revealed marked improvement in four, and slight to moderate improvement in

10; five patients were worse or unchanged. Only 11 were followed up for more than a year. Northfield (1955) has stressed the importance of a neck support being worn by patients who have had an extensive cervical laminectomy, and concluded that patients over the age of 50, or those with more than one disk protrusion, made an unsatisfactory response to operation. Other surgeons, including Allen (1952) and Taylor (1953), have employed more complicated procedures, and have attempted to restore the normal gliding movements of the spinal cord and nerve-roots, which accompany flexion and extension of the neck, by dividing adhesions round the nerve-roots and widening the intervertebral foramina. Finally Frykholm (1951) devised an operation, for the relief of root pain, by which the appropriate intervertebral foramen was unroofed and the root sleeve incised longitudinally to relieve compression.

In the present series 31 patients were submitted to surgery for one or more of the following reasons: (1) When distinction from spinal tumour was uncertain. (2) When myelography showed a spinal block. (3) When medical treatment had failed to arrest deterioration due to a myelopathy, or to relieve severe brachialgia. (4) When the severity of disablement was such that it was felt that medical treatment had little to offer. There were no very definite contra-indications, though in general patients without much disablement, the aged, and those with arterial disease or hypertension, were not treated by surgery.

The nature of the operation. In 29 patients a cervical laminectomy was done: the number of laminae removed was two or three in 15 cases, and four or five in 14. The portion of the ligamentum flavum thereby exposed was resected, and the meningeal envelope opened. In 21 patients between one and four pairs of dentate ligaments were divided. The anterior wall of the spinal canal was inspected and palpated, but no attempt was made to remove centrally placed osteophytic bars. If, however, a part of a protrusion proved to be soft, that portion alone was excised. Dorso-lateral protrusions which caused stretching of a nerve-root were pared down, and local adhesions divided, provided that there seemed to be no danger of thereby injuring the nerve-root and that the abnormality was lateral to the spinal cord. In two patients, who were submitted to operation for the relief of a cervical radiculopathy, the affected nerve-root was approached extradurally by unroofing the appropriate foramen; local adhesions were divided, and osteophytes within the foramen removed; in one patient the root-sleeve was incised by a longitudinal incision.

Results of surgical treatment

Two patients died within 12 hours of operation as the result of pulmonary oedema.

The disturbance of gait. Gait was abnormal in 28 patients, and the severity of the disorder is shown in Table III. In two the defect was slight, and could not be used to assess the effects of treatment; another patient died. Fig. 2 shows the results of follow-up observation of the remaining 25 patients as regards the state of walking. The immediate results were satisfactory, though in the first

three weeks seven patients had a temporary access of neurological signs. After three months 19 were improved, six were unchanged, and one was worse. During the first year two patients died, one of hypertensive cardiac failure, the other of a coronary thrombosis. No autopsy studies were made. Eighteen patients were followed up for one year: 14 were improved, one was unchanged,

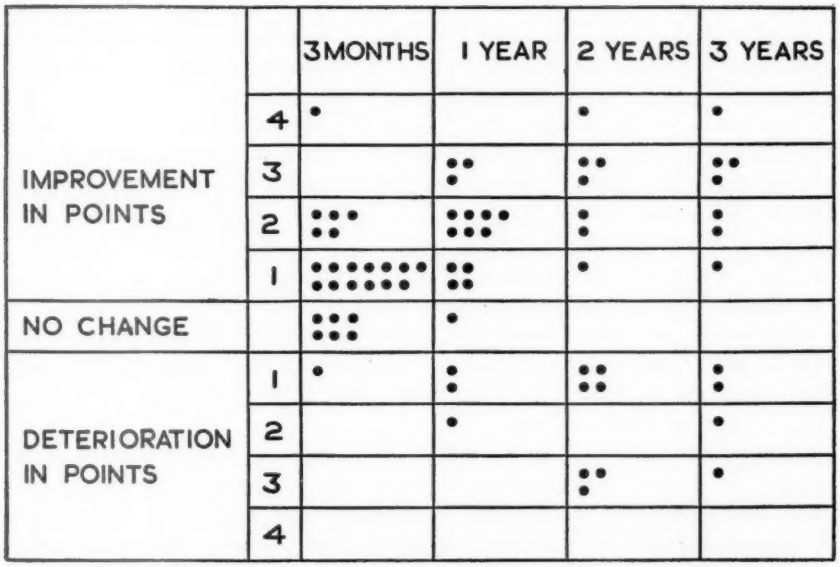

FIG. 2. Scatter diagram showing the results of the follow-up, as determined by the state of walking, in 26 patients with focal spondylosis treated by cervical laminectomy.

and three were worse. Two of the last-mentioned had made a transient improvement, but had deteriorated after six and eight months respectively. In general, the patients with the greatest initial neurological deficit were left with most disability, though the individual extent of improvement was one to three grades, and was not thereby prejudiced, nor was it related to age. Indeed, of the six patients between the ages of 50 and 66, four improved by two grades, one by one grade, and one remained unchanged. This result does not support the contention that age by itself precludes surgery. Though the numbers are small, the duration of symptoms prior to operation seemed relevant, for no patient with a history longer than one year made much recovery. There was no assurance, however, that those with shorter histories necessarily improved. Fourteen patients were followed for two years: seven had deteriorated to below their state immediately before operation, and in seven improvement had been sustained or had increased. The seven who deteriorated had initially improved, but after intervals of between six and 18 months had become rapidly worse, to the point of serious disablement. The pattern of progress was not altered after three years, when 11 patients were examined. The reason for the relapse

was not clear in six of the seven patients, though in one it was related to progressive vertebral subluxation at the site of operation. Their progress was not prejudiced by age (all were under 48 years old), by the duration of symptoms, or by the myelographic appearances, since in five cases only a single indentation of the myodil column was seen. Four showed manometric evidence of a partial spinal block, with levels of between 72 and 112 mg. of protein per 100 ml. in the lumbar spinal fluid. The findings at operation were not remarkable, and in all cases between two and four pairs of dentate ligaments were divided. The most probable explanation, which is purely speculative, is that the deterioration was connected with the development of arachnoiditis.

Root pain. Twelve patients complained of brachialgia, and in four it was a dominant symptom which had not responded to traction or a collar. Of the 10 patients who survived surgery, five were found to have a structural abnormality, which was corrected, to account for their pain; four of these patients obtained complete, and one partial relief. In one patient it proved impossible to decompress an affected nerve-root, and in four no cause for the brachialgia was found; none of these five obtained much benefit.

Impairment of sphincter control. Of the 18 patients who had sphincter disturbances before operation, 15 regained normal control, two were improved, and one was made temporarily worse, though after three months the state found before operation was regained.

Sensory symptoms and signs. Sixteen patients complained of tingling of the finger-tips, and of these five obtained relief, five were slightly better, and six were unchanged. No patient with cutaneous sensory loss within the territory of cervical dermatomes improved, but of the 18 with a level of cutaneous sensory loss over the trunk seven regained normal sensation, and in eight both the density lessened and the upper level receded.

Other observations. None of the patients became normal but, though no measurements were available, spasticity seemed to be reduced and power improved in the lower limbs in those whose walking improved. It is also probable that fasciculation became less prominent, and minor degrees of wasting were reversed.

In summary, the mortality after operation was 10 per cent., and in the survivors the initial results, as judged by the state of walking, were satisfactory. In the majority sphincter control was re-established, and cutaneous sensory loss over the legs and trunk improved. Sensory symptoms and signs in the upper limbs, other than brachialgia, were refractory to treatment. Within six to 18 months about half of the patients who were followed up began to deteriorate, and this tendency continued to the point of serious disability; the reason for this is not clear. When a mechanical cause for brachialgia was detected, its removal relieved the pain, but in four cases no cause was found and little relief was obtained.

The Findings at Operation

After the vertebral spines, together with a portion of the laminae, had been removed, the ligamentum flavum was exposed, and in three cases was reported to be thickened; these patients had shown a posterior filling defect on myelography, probably caused by the thickened ligament. Pulsation of the dural envelope was normal in 28 cases, but in one patient very vigorous arterial pulsations were seen, in association with dense adhesions between the arachnoid and dura. In 24 cases the dura was incised, without nicking the arachnoid, through which it was possible to see the spinal cord; in 10 cases the cord seemed to be displaced very slightly backwards, and in one to be broadened. These findings were minimal and, when the arachnoid was incised, the displacement of the cord subsided as cerebrospinal fluid escaped. There seemed to be plenty of space round the cord, but in one patient with each arterial pulsation it was brought up against an osteophytic bar protruding from the anterior wall of the spinal canal. The dentate ligaments seemed normal, without evidence of tension. Palpation of the anterior wall of the bony canal revealed protrusions, between 0·5 and 1 cm. in width and 2 to 5 mm. in depth, which corresponded in size and site with the myelographic indentations. In 26 patients these ridges were composed of bone-hard material; in three a softer centre was sandwiched between osteophytic lips, and it proved possible to remove the central portion. In one other patient a soft nuclear herniation was completely removed, leaving a hard bar at a lower level. In 10 patients a single nerve-root was stretched over a lateral expansion of a central osteophytic bar, and in five of these cases was bound down by adhesions. In the majority of cases there was some thickening of the arachnoid, which was also adherent to the dura where it was in contact with a protrusion. From this site there extended for a variable distance round the cord a crescent of arachnoidal induration, but this was never sufficient to cause pressure. In most of the patients it was possible to pass a fine instrument between the anterior surface of the cord and the projecting osteophytic bar. In three patients flexion and extension of the neck, after the meningeal envelope had been opened, did not cause any pressure to be brought to bear on the spinal cord.

The Pathogenesis of Myelopathy in Cervical Spondylosis

A number of examples have been described which indicate that changes in the cervical cord may arise from the direct pressure exerted by spinal osteophytes (Stookey, 1928; Bedford, Bosanquet, and Russell, 1952; Brain, Northfield, and Wilkinson, 1952; Clarke, 1955). But the symptoms and signs often suggest affection of the posterior or lateral columns, which are regions far removed from the site of the compression. Kahn (1947) and Bucy, Heimburger, and Oberhill (1948) have tried to explain the location of the neural lesions on the basis of a pressure-wave set up by the attachments of the dentate ligaments; these structures prevent dorsal displacement of the spinal cord, and may themselves be thickened in association with cervical spondylosis (Bedford,

Bosanquet, and Russell, 1952; Brain, Northfield, and Wilkinson, 1952). Observations in the present series have not suggested that pressure upon the spinal cord is a dominant factor, nor was tension evident in the dentate ligaments. Although there was slight dorsal displacement of the cord *in situ*, when the arachnoid was incised its position was restored to normal as cerebrospinal fluid escaped, while there always seemed to be plenty of room anterior to the cord. Love and Walsh (1940) found thickening of the ligamentum flavum at operation in cases of cervical spondylosis; this condition was also found in three patients in the present series, and had been suspected from the appearances of the myelogram in another case. A post-mortem examination was described by Taylor (1953) in which forward bulging of the ligamentum flavum had lacerated the posterior columns of the spinal cord; but there is not much evidence that this mechanism plays an important role in the production of the myelopathy of cervical spondylosis. Ricard and Masson (1951) have drawn attention to the frequency with which adhesions are found at autopsy in patients with cervical spondylosis, involving both the arachnoid and the dura, but in the present series they were never of a degree likely to be of great aetiological importance. Frykholm (1951) has shown that flexion and extension of the neck are accompanied by gliding movement of the spinal cord and nerve-roots within the theca. He demonstrated that fibrosis of the root sleeves modified movement by anchoring the roots to their meningeal sleeves, and these in turn to the bony canal. Many have considered that this abnormality might be responsible for the myelopathy of cervical spondylosis. Little information can be derived from the observations made at operation in the present series, for the exposure did not permit inspection of the root-sleeves within their foramina. In three patients flexion and extension of the neck, after the theca had been opened, failed to show any tethering or restriction of movement. Other observers, unimpressed with the mechanisms hitherto invoked, have incriminated vascular factors. Haglund (1942) described an autopsy on a patient with cervical spondylosis, at which he found compression of a vertebral artery by spinal osteophytes; and Brain, Northfield, and Wilkinson (1952), in a similar case, reported displacement of the anterior spinal artery, though they were not impressed by its possible aetiological significance. Mair and Druckman (1953) concluded that the autopsy findings in two patients were compatible with compression of the anterior spinal artery and ischaemic change within the territory supplied by this vessel. Lastly, Girard, Garde, and Devic (1954) have described pathological changes in the brain-stem and spinal cord, attributable to hyaline degeneration of the smaller intramedullary arteries in the presence of cervical spondylosis, without evidence of compression of the cord.

It is not possible to come to any definite conclusion with regard to the pathogenesis of myelopathy in cervical spondylosis. All that can be said with certainty is that evidence of compression is frequently lacking at operation, and there does not seem to be any tension upon the dentate ligaments, nor are adhesions seen to constrict or bring pressure to bear upon the spinal cord. Suh and Alexander (1939) have reminded us that the blood-supply of the cervical cord is derived

from two, or at the most three, unpaired radicular arteries, the remainder being too small to make any significant contribution. Thus, if one of these vessels was compressed in the appropriate foramen by osteophytes or by adhesions associated with root-sleeve fibrosis, between one-half and one-third of the blood-supply to the cervical cord might be imperilled. If this contention were true it would explain the discrepancy between the radiological and clinical findings so often found, for the nature of the neurological deficit would then depend on whether or not a major radicular artery were compressed.

Discussion and General Conclusions

During the past five years the diagnosis of cervical spondylosis has been made with increasing frequency, and its incidence as a cause of myelopathy would appear to be almost equal to that of disseminated sclerosis. Evidence both from the present series and from previous reports suggests that about 65 per cent. of people over the age of 50 have such spondylosis without neurological symptoms or signs. It must be expected, therefore, that the radiological abnormality will be associated with other causes of myelopathy, and may be of no pathological significance. Further, it has been shown that there is seldom correlation between the magnitude of the radiological findings and the extent of the neurological deficit, and the demonstration by myelography of protrusions from the anterior wall of the spinal canal gives no assurance that they are relevant to the neurological diagnosis. In six (10 per cent.) of 61 patients in the present series, events within the subsequent three years indicated that the neurological deficit was due to another cause. It is probable that with the passage of time further diagnostic errors will be exposed. There seems to be an eagerness to affix the label 'cervical spondylosis' to every patient past middle age who has spinal neurological signs the cause of which is not immediately apparent.

The diagnostic problems related to cervical spondylosis have been presented and discussed. The clinical syndromes associated with that condition may resemble those of spinal tumour, motor-neurone disease, disseminated sclerosis, syringomyelia, and the thoracic inlet syndrome. The greatest help in differential diagnosis is provided by attention to clinical detail. Examination of the lumbar cerebrospinal fluid in patients with cervical spondylosis may show an increase of protein up to 120 mg. per 100 ml. without manometric or myelographic evidence of spinal block. The appearances at myelography may also be misleading, and may suggest either an intramedullary or an extramedullary tumour of the spinal cord by the presence of a posterior filling defect, broadening of the normal ribbon of translucency due to the position of the spinal cord, or the position of the anterior indentation, which may be opposite to a vertebral body rather than to a disk space. The filling defect probably arises from thickening and plication of the ligamentum flavum, the broadening from slight pressure upon the anterior surface of the cord, and the site of indentation from displacement of a previous soft nuclear herniation by the posterior longitudinal ligament, so that it comes to lie adjacent to a vertebral body.

The insistence on myelographic or surgical confirmation of the pathology in the present series has imposed a bias by selecting the more seriously disabled patients. In this way a large number of cases of slight neurological deficit, in which myelography was considered unjustifiable, was excluded, and the series is not a representative sample of the disease. A study of these milder cases has shown that a benign form of cervical spondylosis exists, with neurological complications which are arrested, spontaneously or by treatment, short of serious disablement, though of course the diagnosis remains open to doubt. Certainly the gross restriction of gait, by which 20 patients could walk only 300 yards with the aid of two sticks, and the fact that 19 exhibited a level of cutaneous sensory loss over the trunk, and 24 had impairment of sphincter control, represents a disablement beyond usual experience.

The aetiological role of antecedent trauma has been investigated, and the evidence suggests that it is concerned with the production of a nuclear herniation, which later gives rise to a focal spondylosis. This contention is supported by the development of focal spondylosis after experimentally produced nuclear herniation, the finding at operation of all stages between the soft nuclear herniation and the hard osteophytic bar, the frequency with which a history of trauma is evident in patients with focal spondylosis, and the lapse of time often found between injury and the onset of disability. It is also apparent that, when there is pre-existent cervical spondylosis, an injury may precipitate a profound neurological deficit, which cannot always be explained by a traumatic nuclear herniation superimposed upon the degenerative disease. The pathogenesis of this access of disability remains undetermined. The importance of occupational stress is suggested by the preponderance of male patients, the later age at the onset of symptoms in women, the high incidence of occupational stress in the present series, and the site most often affected (C5–6), which contributes most to flexion and extension of the cervical spine. A survey of 50 patients has suggested that occupational stress does not increase the liability to cervical spondylosis, but that it predisposes to neurological complications if spondylosis already exists. Thus the radiological detection of spondylosis might be an indication for the removal of the patient from conditions associated with stress.

Until now there has been no presentation of the results of medical and surgical treatment of a large series of patients followed up for two years. Twenty-six patients with myelopathy are described who were treated medically and followed up for such a period. Examination of 15, who had focal spondylosis, showed that 12 were improved, two were unchanged, and one, who had sustained a fall, had deteriorated. Of the 11 patients with generalized spondylosis four were unchanged, and seven had deteriorated to the point of serious disablement. A review of possible factors responsible for this result indicated that prognosis was related to the number of disk protrusions rather than to age or the duration of symptoms. It is not possible to say whether the wearing of a polythene collar was responsible for such improvement as did occur, for medical treatment included exercise therapy, mephenesin carbamate to reduce spasticity, and the fitting of surgical appliances. There was strong presumptive evidence that a

collar was beneficial, for it was the only method of treatment common to all these medical patients, and three, who received no other treatment, became normal. In addition, root and neck pain, which had often been present for months, was relieved in 11 cases within an average of six weeks.

Thirty-one patients were submitted to laminectomy, and the mortality was 10 per cent. The initial results were encouraging as measured by the improvement of gait: only one patient was made worse by operation, six were unchanged, and 19 improved. Between the sixth and 18th months, however, seven, who had made an initial improvement, deteriorated rapidly, to the point of serious disablement by the end of two years; in the remainder improvement was sustained or increased. There was no evidence that age influenced the results of surgery, though little improvement occurred in patients with a history of more than a year. Relapse after initial improvement was related to vertebral subluxation in one case, but in the remainder no cause was identified, though it is possible that arachnoiditis was responsible. When operation revealed a cause for brachialgia, and the cause was removed, the pain was invariably relieved, but in four cases no mechanical compression of nerve-roots was found, and little relief was gained.

The results suggest that if a patient with generalized spondylosis continues to deteriorate in spite of wearing a collar, he should be submitted to surgery without delay. The best results are obtained if the duration of symptoms before operation is short, and to postpone a decision beyond a year is to prejudice the outcome. Provided the initial disability is not too great, patients with focal spondylosis do fairly well when treated with collars. The pathogenesis of the myelopathy associated with cervical spondylosis remains in doubt, but the observations at operation in the present series indicate that direct compression of neural structures within the spinal theca is uncommon. It is suggested that of one of the three main radicular arteries which contribute to the anterior spinal artery may be compressed by osteophytes or adhesions within the appropriate intervertebral foramen.

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Summary

1. The clinical features of 78 patients with cervical spondylosis and a neurological deficit are presented, analysed, and discussed.

2. Problems related to differential diagnosis are described. The myelographic demonstration of cervical spondylosis gives no assurance that any neurological

deficit is thereby caused; and the neurological complications of cervical spondylosis may be mistaken for other disease.

3. Subsequent events exposed an erroneous diagnosis in six patients.

4. The protein level in the lumbar cerebrospinal fluid may be as high as 120 mg. per 100 ml. in the absence of a manometric abnormality.

5. Myelography may reveal a posterior filling defect, widening of the ribbon of relative translucency due to the spinal cord over a few segments, or an anterior indentation adjacent to a vertebral body rather than to a disk space.

6. The evidence suggests that focal spondylosis arises from a traumatic nuclear herniation.

7. Deterioration of myelopathy due to cervical spondylosis occurs after trauma, and is not always related to a nuclear herniation.

8. Occupational stress does not predispose to cervical spondylosis but, if this condition exists, increases the liability to neurological complications.

9. Patients with myelopathy due to focal spondylosis improve, or remain unchanged, when treated with collars; those with generalized spondylosis most often deteriorate. The majority of patients with brachialgia obtain some relief within days, and complete relief within weeks, of assuming a collar.

10. The short-term results of surgery are satisfactory, but about half of the patients with myelopathy deteriorate after six to 18 months. The reason for this is not clear. The degree of improvement is not related to age or the number of disk protrusions, but few patients with a history longer than one year made a significant recovery. If a mechanical cause for brachialgia is found and corrected at operation, relief from pain is the rule; if none is found, amelioration is uncommon.

11. The pathogenesis of myelopathy associated with cervical spondylosis is seldom related to direct compression of the spinal cord, and remains in doubt.

12. Cervical spondylosis is being diagnosed with increasing frequency, often without justification; in six patients in the series the original diagnosis of the cause of their disability was refuted by subsequent events, in spite of myelographic confirmation of the spondylosis.

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CARCINOMA OF THE THYROID[1]

A Review of 100 Cases

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With Plates 22 and 23

THE importance of carcinoma of the thyroid is much greater than its incidence would suggest; it is a rare tumour, causing only 0·4 per cent. of all deaths from malignant disease (Registrar General's Report, 1954). There are several reasons for the interest which a tumour in this site arouses. In a centre which is dealing with a large number of the commoner thyroid disorders, the possibility of the presence or development of a carcinoma has always to be considered, especially as this condition is less selective in its age incidence than most other tumours, and is relatively frequent under the age of 40 years. Furthermore, modern methods of diagnosis and treatment make increasing use of ionizing radiations, which may themselves play a part in the genesis of thyroid carcinoma (Duffy and Fitzgerald, 1950; Simpson, Hempelmann, and Fuller, 1955; Clark, 1955). We have accordingly reviewed a series of cases of thyroid carcinoma which have been diagnosed since 1946, when radioiodine became available in this country for the investigation and treatment of thyroid disease. Few British reports on carcinoma of the thyroid have appeared recently (Branson and Houston, 1949; Alhadeff, Scott, and Taylor, 1956), in contrast with the numerous reports from the United States of America (Clute and Warren, 1935; Pemberton, 1939; Horn, Welty, Brooks, Rhoads, and Pendergrass, 1947; Frazell and Foote, 1949; Beahrs, Pemberton, and Black, 1951; McDermott, Morgan, Hamlin, and Cope, 1954; Sloan, 1954). It is clear that geographical factors may produce striking differences, an illustration being the high incidence of carcinoma in nodular goitre from endemic goitre regions (Majarakis, Slaughter, and Cole, 1953). This fact has encouraged us to review the present series of cases from the Sheffield region, where goitre is relatively common. Particular attention has been paid to the biological characteristics of the different histological types of thyroid carcinoma, and to the association of carcinoma with simple goitre, thyrotoxicosis, and previous exposure of the neck to ionizing radiations.

Patients Studied

The series comprises the patients referred to the Sheffield National Centre for

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Radiotherapy since 1946. In all there were 103 patients, but three were excluded when the histological findings were reviewed, leaving a total of 100 (Table I). Forty-six were alive in 1955; 40 of these have been seen and examined for any recurrence of growth, and their state as regards thyroid function assessed. The other six patients were unable to attend for review, but a report was obtained on their condition. Survival statistics are given for the period from the date of treatment to the end of 1955. Tissue for histological examination was not obtained from 22 patients. There were strong clinical grounds for diagnosing thyroid carcinoma; and because the purpose of this review is to discuss a series of cases of thyroid carcinoma which are not selected in any way, apart from being referred to a Radiotherapy Centre, and since the omission of 22 per cent. of a series would at once produce a selection bias, these patients have been included, but considered separately whenever possible.

Criteria for diagnosis of carcinoma. The only reasonably certain evidence of carcinoma of the thyroid is spread of the tumour tissue outside the confines of the gland. Local invasion of surrounding structures, such as muscle, trachea, and oesophagus, may be found at operation, but this finding is sometimes confused with chronic thyroiditis. Local recurrence of a mass is strong evidence of malignancy, especially if histological examination of the original tissue suggested carcinoma. Though a thyroid adenoma may recur, histological findings, particularly the lack of invasion of capsule and veins, help to establish the diagnosis. Finally, the presence or development of metastases is clear evidence that the tumour is malignant. Although each of these points makes the presence of a carcinoma reasonably certain, histological examination of tissue is required to confirm the origin of the tumour. By considering together the pathological spread and the microscopic appearances, the series may be divided into the following groups.

1. *Carcinoma, thyroid in origin.* In this group, 67 per cent. of the total number of cases, at least one of the above features of malignancy was present, and histological examination confirmed the belief that the tumour arose in the thyroid.

2. *Probably carcinoma, thyroid in origin.* In 11 cases the diagnosis of carcinoma was made from the examination of tissue removed from a swelling in the thyroid. The histological criteria for this diagnosis will be considered later, but thyroid carcinoma is notoriously difficult to diagnose solely on histological grounds (Graham, 1924). Thus the findings in these cases are only presumptive of carcinoma, pending the development of more certain evidence of malignancy.

3. *Carcinoma, probably thyroid in origin.* This group comprises the 22 cases in which no tissue for histological examination was obtained. They all showed local recurrence or metastases during the course of the disease, and the evidence of malignancy is thus very strong; but the evidence of a thyroid origin is entirely clinical.

Clinical Features

Age and sex distribution. Women comprised 80 per cent. of the whole series

(Table I). Harnett (1952) and Sloan (1954) found the same ratio of female to male patients. Beahrs, Pemberton, and Black (1951) found a lower ratio (2 : 1),

TABLE I

The Distribution of 100 Cases of Thyroid Carcinoma by Sex, Histological Confirmation, and other Thyroid Disease

	Total	*Men*	*Women*
Whole series	100	20	80
With histological evidence of thyroid carcinoma	78	17	61
Without histological evidence of thyroid carcinoma	22	3	19
With history of previous goitre for more than 5 years	18	2	16
With coexistent hyperthyroidism and thyroid carcinoma	7	—	7

and Pemberton (1939), reviewing 774 cases, noted a ratio of only 1·7 : 1. McDermott, Morgan, Hamlin, and Cope (1954) observed a striking difference in sex incidence only among patients with differentiated tumours; this point will be considered more fully in discussing the features of histological types of thyroid carcinoma. The mean age of the whole series of patients was 54·9 years, with no difference between the sexes (Table II). The mean age of the patients in whom

TABLE II

The Age Distribution of 100 Cases of Thyroid Carcinoma

		Mean age (years) ± standard error		
	Total	*All patients*	*Men*	*Women*
Whole series	100	54·9±1·5	54·0±3·7	55·1±1·7
With histological evidence of thyroid carcinoma	78	51·5±1·4	50·8±3·3	51·7±1·6
Without histological evidence of thyroid carcinoma	22	66·8±2·7	..	65·9±2·8
With previous goitre for more than five years	18	53·7±3·6	..	55·2±3·7

no histological evidence of the thyroid origin of the malignant disease was obtained was higher than the mean age of the whole series.

Presence of other thyroid disease. A number of patients showed evidence of thyroid disease apart from carcinoma (Table I). Previous goitre was only recorded if the patient gave a history of thyroid swelling for more than five years before the development of symptoms suggestive of carcinoma. Similarly, coexistent hyperthyroidism was only diagnosed when certain strict criteria were fulfilled. Both of these associations will be described fully in later sections. In addition there was one case of hypothyroidism and carcinoma. This occurred in a girl of 27 years, who from an early age had had numerous operations for goitre. She had developed hypothyroidism, and some years later a thyroid swelling recurred, which was found to be a follicular carcinoma.

Initial symptoms. The first symptoms noted by each patient are shown in Table III. Patients with a previous goitre are treated separately, since local

symptoms are often neglected when the patient already has a thyroid swelling. Symptoms referable to the neck predominated. In only five per cent. of the whole series was the first symptom remote from the thyroid, and these five patients all had pain or pathological fracture from a bony metastasis. In six per cent. enlargement of one or more cervical lymph-glands was the first complaint. These cases correspond to those formerly classified as lateral aberrant

TABLE III

Initial Symptoms in 100 Cases of Thyroid Carcinoma

	Without previous goitre		*With previous goitre*	
	Men	*Women*	*Men*	*Women*
Total number	18	64	2	16
Swelling of thyroid	15	52	..	..
Increase in size of previous goitre	..	..	1	8
Swelling of cervical lymph-glands	2	4	..	1
Pressure symptoms in neck	1	..	1	3
Symptoms referable to hyperthyroidism	..	5	..	2
Symptoms referable to osseous metastases	..	3	..	2

tumours, but a primary thyroid carcinoma was always present. Pressure symptoms have been striking by their rarity, especially in patients without previous goitre. The majority of patients with associated hyperthyroidism also complained of a swelling in the neck.

Clinical diagnosis of thyroid carcinoma. The present series illustrates the fact that in many cases, which later prove to be malignant, a clinical diagnosis of thyroid cancer cannot be made. Suspicious features are a hard and irregular swelling, fixation to surrounding structures, rapid increase in swelling, especially if producing pressure symptoms, and vocal cord paralysis. More certain criteria are cervical gland enlargement and evidence of remote metastases. The 22 cases lacking histological corroboration of the thyroid origin of the tumour all showed the above local features, and many showed evidence of local or remote metastases. In 31 of the remaining 78 cases, however, the initial clinical diagnosis was a benign lesion, but after surgical treatment histological examination revealed a carcinoma. In 20 cases the diagnosis was first suggested at operation, by the discovery of local invasion and metastases in cervical glands. Thus the finding of a thyroid swelling which is not hard, irregular, or fixed is of no practical value in excluding thyroid carcinoma.

Metastases. The incidence and sites of metastases are shown in Table IV. They are divided into metastases found when the patient was first seen, and those developing thereafter. Slightly more than half of the total series of patients showed evidence of metastases, and this proportion is not significantly changed when related to histological evidence of thyroid cancer or to the presence of previous goitre. Spread to cervical lymph-glands was commonly present when the patient was first seen, and developed in an appreciable number thereafter. Remote metastases were not common initially, but became evident later, especially in the lungs and bones.

TABLE IV

Cases of Thyroid Carcinoma with Metastases

Group	Number of patients	Number with metastases present at various sites at time of diagnosis					Number with metastases developing at various sites after diagnosis and treatment							Number of patients with mestastases at any time
		Cervical glands	Pulmonary	Osseous	Other sites	Total number with metastases	Cervical glands	Pulmonary	Osseous	Hepatic	Cerebral	Other sites	Total number with metastases	
With histological evidence of malignancy . . .	78	17	2	4	..	23	9	12	9	4	3	9	30	47
Without histological evidence of malignancy . . .	22	3	1	3	1	8	1	3	..	..	..	..	4	12
Without previous goitre .	82	18	2	4	..	23	8	13	8	3	3	5	29	48
With previous goitre . .	18	2	1	3	..	6	2	2	1	1	..	4	5	11

Characteristics of Different Histological Types

Classification. The histological types of tumour from the 78 patients from whom tissue had been obtained by biopsy, at operation, or at subsequent autopsy, were classified according to the system of Willis (1953). Tissue for such re-assessment could be obtained in only 70 cases. In the remaining eight cases the initial microscopic reports described a carcinoma, and the features diagnostic of malignancy, mentioned above, were also present; the original reports on the histological examination were accordingly used in classifying them. It is unlikely that such a small percentage would change the overall picture. It was found that all cases fitted into the following classification, which is a simplification of that given by Willis (1953).

A. Differentiated tumours:
   (1) Papillary carcinoma
   (2) Follicular carcinoma
   } with or without colloid formation.

B. Undifferentiated tumours:
   (1) Small-cell carcinoma. (2) Large-cell carcinoma.

C. Rare tumours: (1) Epidermoid carcinoma. (2) Fibrosarcoma.

The sections were assessed in the following manner. All were examined by one of us (R.K.), without knowing the previous histological diagnosis, and classified as above. The results were then compared with the previous opinions. Cases in which evidence, other than histological, of malignancy existed, and in which the two opinions were the same, were then accepted as classified. The histological slides from the remaining cases were then examined by Professor D. H. Collins. They comprised the 11 cases without other evidence of malignancy, the cases in which the two opinions differed, and the cases of coexistent thyrotoxicosis and thyroid carcinoma. In the final assessment only 10 cases were placed in a different histological group, so that substantial agreement was reached with the original opinions. The tumours were classified according to the predominant histological type seen in the primary lesion in the thyroid. Like so many other tumours, thyroid carcinoma may present a variable histological picture in the same tumour, and occasionally metastatic deposits may differ from the primary thyroid tumour. In the present series the tumour was graded according to the histological appearance of a metastasis only in the two cases in which tissue from the primary tumour was not available.

As already stated, in 11 cases there was no evidence of malignancy other than a swelling within the thyroid, from which sections had been taken. Such lesions present great difficulties in diagnosis when the histological picture is papillary in type. Most pathologists follow the opinion of Willis (1953) that papillary adenoma cannot be distinguished from papillary adenocarcinoma on histological grounds. Graham (1924) suggested the criteria of capsular invasion and invasion of blood-vessels for deciding malignancy in such lesions, and this principle was also stressed by Vaux (1937). Warren (1931) has raised doubt

about the validity of such criteria. In the final estimate these 11 cases were accepted as examples of carcinoma because there was gross capsular invasion and the usual morphological criteria of carcinoma cells were satisfied. Three other cases, rejected from the series, showed retention of the tumour within a capsule, and the appearance of the cells was not definitely carcinomatous.

Relative incidence (see Table V and Fig. 1). Papillary carcinoma (Plate 22, Fig. 2) comprised the largest group (45 per cent.) among the 78 cases. This has been the usual finding in most large series which have been reported, such as those of Frazell and Foote (1949) and Cope, Dobyns, Hamlin, and Hopkirk (1949). As no difference in any characteristic examined was found between small-cell and large-cell undifferentiated carcinomas, these have been grouped together, and comprise 30 per cent. of the cases (Plate 22, Fig. 3). Follicular carcinoma (Plate 22, Fig. 4) was the smallest of the main groups (23 per cent.). At variance with these results, and with most other series, are those of Alhadeff, Scott, and Taylor (1956), who found follicular carcinoma to be the commonest type.

Sex incidence. The female preponderance in the series as a whole is retained in each histological type (Table V). The female : male ratio is increased in follicular carcinoma, and decreased in undifferentiated carcinoma. This finding in the latter type of tumour has been frequently noted (McDermott, Morgan, Hamlin, and Cope, 1954).

The mean age is strikingly different in each group (Table V). The age incidence of papillary carcinoma is significantly different from that found in the follicular and undifferentiated types. Comparing the papillary and follicular groups, $t = 2{\cdot}6$, and $P < 0{\cdot}02$. When the papillary and undifferentiated groups are compared, $t = 3{\cdot}90$ and $P < 0{\cdot}001$. The fact that thyroid carcinoma may occur in young persons is well known, but it is obvious that such patients usually have a papillary carcinoma. Of the whole series of 100 patients, 18 were 40 years old or younger, and in 16 of these the growth was papillary in type. The fact that young people develop papillary carcinoma is also well attested by Black (1947) and Crile (1950). This type is not found exclusively, however, in the younger age-groups, for 19 of the patients with papillary growths were over the age of 40 years. The mean ages of the groups with follicular and undifferentiated carcinoma fall into the usual age range for cancer.

The survival of different groups cannot be discussed except in relation to the survival data of the whole series, and to the results of different forms of treatment. The five-year survival rate has been used for purposes of comparison, and for this comparison the patients fall into the usual groups: 'alive without evidence of tumour,' 'alive but with tumour present,' and 'dead with tumour present.' No patient died apparently free from tumour, so that deaths from intercurrent diseases are not considered. The expected five-year survival rates of different groups have been calculated from life expectancy tables (*Annual Abstract of Statistics*, 1948) and are shown in Tables V and VI. Table VI gives the results, as regards survival, in the whole series and in particular groups.

TABLE V

Classification of 78 Cases of Thyroid Carcinoma by Histological Type of Tumour related to Age, Sex, and Survival

Predominant histological type of tumour	*Number of patients*	*Number with evidence, other than histological, of carcinoma*	*Male: female ratio*	*Mean age at diagnosis (years) and standard error*	*Number dead as percentage of total*	*Average survival time of those dead (years)*	*Expected survivors %*	*Crude 5-year survival rate % and standard error*
Papillary	35	28	1 : 4	44·8±2·8	23	3·1	*93·6*	73·5±7·5
Follicular	18	16	1 : 8	55·2±2·5	67	4·8	*91·7*	54·5±11·7
Undifferentiated	23	21	1 : 2·3	60·1±2·2	70	1·3	*86·7*	16·7±7·8
Rare {Epidermoid	1	2	..	..	..	..	..	..
Rare {Fibrosarcoma	1							

TABLE VI

Survival rates of 53 Patients with Thyroid Carcinoma

	Possible survivors after 5 years	*Actual number surviving after 5 years*	*Surviving after 5 years without tumour*		*Expected 5-year survivors (%)*	*Died after 5 years, with tumour*	*Number surviving to date*
			Number	*% and standard error*			
Whole series	53	25	22	41·5±4·9	*88·1*	8	17
With histological evidence of thyroid tumour	45	23	20	44·5±5·6	*91·4*	7	16
Papillary	15	13	11	73·5±7·5	*93·6*	3	10
Follicular	11	6	6	54·5±11·7	*91·7*	3	3
Undifferentiated	18	4	3	16·7±7·8	*86·7*	1	3
Other	1	..	..	..	..	..	..
Without histological evidence of thyroid tumour	8	2	2	25·0±9·2	*77·0*	1	1
Treated by operation and deep X-ray therapy	25	14	13	52·0±7·4	*90·5*	3	11
Treated by deep X-ray therapy	22	5	4	18·2±6·8	*82·4*	2	2
Others	6	..	..	..	..	..	..

Patients who survived for five years and died later are also included, so that the final column shows the number surviving for a variable period after five years. In Fig. 1 all the cases except the two rare tumours are included, and the survival of the patients is shown up to the end of 1955. The mean survival times of patients who died have been calculated for the various groups, and are shown in Table V.

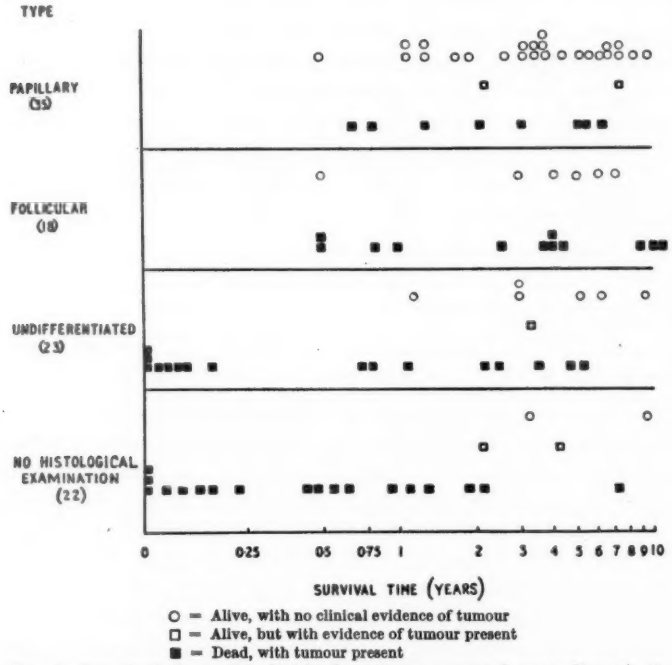

FIG. 1. Survival time of individual patients grouped according to the histological type of thyroid carcinoma.

Fifty-three patients began treatment before the end of 1950 (Table VI). Twenty-five survived for more than five years, and 22 (41·5 per cent.) were alive and showed no evidence of the presence of tumour. Of the 25 patients, however, who were alive five years after treatment, eight died later with a tumour present. Thus it is clear that five-year survival figures are of little value in assessing the treatment of thyroid carcinoma. This fact has been emphasized by McDermott, Morgan, Hamlin, and Cope (1954), and Ward (1949). When the results from different groups are considered, there are wide divergencies in survival rates. The five-year survival rate for patients with papillary carcinoma was 73·5 per cent., and the mean survival time for those who had died was 3·1 years. This result is in striking contrast to the outcome among patients with undifferentiated tumours, whose five-year survival rate was only 16·7 per cent., and mean survival time, for those who had died, only 1·3 years. Cases of follicular carcinoma were intermediate between these two groups in respect of

five-year survival, but the mean survival time was longer than in papillary carcinoma. The differences between these three groups are significant at the 5 per cent. level. When the expected five-year survival from life tables is taken into account, the difference between cases of papillary and follicular carcinoma is on the borderline of significance. The fate of patients with undifferentiated tumours was very similar to that of patients in whom histological corroboration

TABLE VII

Treatment of 100 Patients with Thyroid Carcinoma, Classified by Histological Type of Tumour

	Operation and deep X-ray therapy	*Deep X-ray therapy*	*Operation*	^{131}I	*No treatment*
Number of patients	46	32	11	6	5
5-year survival per cent.	52	18	..	..	..
Type of tumour:					
Papillary	27	1	6	1	..
Follicular	7	3	2	5	1
Undifferentiated	12	9	2	..	..
No histological examination	..	18	..	..	4
Others	..	1	1	..	..

of thyroid carcinoma was lacking. The five-year survival rate in the latter group was 25 per cent., and the mean survival time of those who had died was only 0·8 year. The majority of patients having undifferentiated tumours, or tumours not histologically examined, died within 12 months of treatment (Fig. 1). Those surviving this period lived for variable periods during the following few years. The similarity suggests that the majority of the patients in whom no histological evidence was obtained had in fact undifferentiated tumours. The differences in survival according to histological type of tumour are also reflected in the survival results after different forms of treatment, as shown in Table VII. The majority of patients were treated either by operation followed by deep X-ray therapy, or by deep X-ray therapy alone. The low five-year survival rate after treatment by deep X-ray therapy is explicable when it is seen that, in 84 per cent. of the patients so treated, either the tumour was undifferentiated or its type was not known. No comparison of treatments can be made when such a bias of selection has been present. Deep X-ray therapy was used alone when the patient was too ill, or the tumour too advanced, for operation. To a large extent this fact would also account for the failure to obtain tissue for histological examination.

The above findings as regards survival are similar to previous reports. McDermott, Morgan, Hamlin, and Cope (1954), Frazell and Foote (1949), and Dunhill (1931–2) have stressed the high survival rates for papillary carcinoma, and the very poor results for undifferentiated tumours.

It is impossible to ascertain how far these results are due to treatment, as there are no control groups for comparison. Only patients with papillary carcinoma have a good expectation of life. But it is this particular type of tumour

which creates the greatest difficulties for the pathologist in deciding whether it is malignant. Ten patients out of 15 with papillary carcinoma survived more than five years. Seven of these patients showed evidence, other than histological, of malignant disease, and even in them the survival rate was high. Sloan (1954) reported similar differences in survival according to the type of tumour, but also found that the chance of survival with a particular type decreased with increasing age at diagnosis. The results from the present series do not suggest this tendency, but the groups are smaller than those reported by Sloan.

Occurrence of metastases. No striking differences in the development of metastases were noted between the histological types of tumour, with the possible exception of metastases in bone. Eleven patients with morphological evidence of thyroid carcinoma developed osseous metastases. Five of these, or nearly 50 per cent., had follicular carcinoma (Plate 22, Fig. 5). This predilection of follicular carcinoma to produce bony metastases was reported by Frazell and Foote (1949).

Radioiodine Investigation and Treatment

Patients were selected for radioiodine investigation almost entirely according to the histological type of tumour. Other factors influencing this selection were related to their clinical state. An inoperable tumour, the presence of metastases, and recurrence following primary treatment were all reasons for deciding on ^{131}I investigation. Concentration of ^{131}I by tumour tissues was investigated in two ways. Uptake measurements were made over the mass in the neck, or over areas where metastases were present. Alternatively, or in addition, some of the suspected tumour tissue was removed 48 hours after ^{131}I was given, and the ^{131}I content was measured by liquid counting, and expressed as μc. per gm. of tissue. The tissue was also examined histologically and autoradiographs were made in some instances (Plate 23, Figs. 6 and 7). If the tissue removed was malignant, this method gave a direct estimate of the ability of the tumour to concentrate ^{131}I. The interpretation of results from *in vivo* counting had certain inherent difficulties. It gave definite evidence of ^{131}I concentration when the region counted normally showed little or no concentration; but in regions where iodide concentration takes place it may be difficult to assess the activity of a tumour mass. This difficulty applies to the liver and stomach, and also to the neck, wherever normal thyroid tissue may be present. Thus, measurement of concentration of ^{131}I in a discrete lump in the thyroid is difficult because of the surrounding activity. The results of investigations with ^{131}I may be classified as follows:

1. *Tumour probably not concentrating radioiodine.* Into this category fall those cases in which very little activity was found in resected malignant tissue. Those in which no concentration was found by *in vivo* counting are also included.

2. *Tumour apparently not concentrating* ^{131}I, *but results not decisive.* This class includes cases in which no concentration was demonstrable by *in vivo* counting, but high activity was present in surrounding structures, usually from the other

parts of the thyroid. Cases in which measurements were made after treatment are also placed in this group. In these cases lack of concentration may be explained by complete removal or destruction of the tumour tissue.

3. *Tumour certainly concentrating* ^{131}I *to some extent.* Appreciable activity in resected tissue made this certain, and *in vivo* counting clearly demonstrated concentration.

Table VIII shows the results of ^{131}I investigation in 37 cases. Concentration by the tumour was definitely found in only seven patients; five of these had

TABLE VIII

Results of ^{131}I *Investigation in 37 Cases of Thyroid Carcinoma*

	Number of patients	*Type of tumour*			
		Papillary	*Follicular*	*Undifferentiated*	*No histological examination*
	37	19	11	3	4
No demonstrable ^{131}I concentration in tumour	11	9	2	..	..
No demonstrable ^{131}I concentration, but (*a*) thyroid present, or (*b*) after treatment	19	8	4	3	4
Demonstrable ^{131}I concentration in tumour	7	2	5	..	..

follicular carcinoma, and two had papillary carcinoma. Thus nearly half of those patients with follicular carcinoma who were studied showed demonstrable concentration. This result is to be expected from the morphology of follicular carcinoma, as has been repeatedly shown by other investigators (Dobyns and Maloof, 1951; Rawson, Rall, and Peacock, 1951; Cunningham, Hilton, and Pochin, 1955; Kramer, Concannon, Evans, and Clark, 1955). A papillary carcinoma may also occasionally concentrate ^{131}I. The two examples in the present series showed formation of colloid in the papillary structure.

Table IX shows some of the data regarding the six patients who were treated with large doses of radioiodine. So far only one patient (Case R1) has had apparently complete destruction of her tumour, and it is of interest that she was a young girl of 17 years with a papillary carcinoma (Plate 23, Fig. 8). Cases R5 and R6 showed radiological evidence of destructive effect on some metastases, while other metastases were unaffected. The effect was only temporary. Cases R1, R5, and R6 have been described more fully elsewhere (Blomfield, 1949–50, 1953). Thiouracil and thyrotrophic hormone were given to some patients in an attempt to produce concentration, but with no success.

Relation to Previous Goitre

Eighteen patients (18 per cent.) gave a history of previous swelling in the region of the thyroid gland for at least five years. In only three had the swelling been present for less than 10 years; in two the tumours were thought to be simple non-toxic goitres, and carcinoma was found when operation was performed; the third patient had thyrotoxicosis when she was first seen, and is described with the other cases of coexistent hyperthyroidism and carcinoma.

TABLE IX

Results of ^{131}I Therapy in Six Cases of Thyroid Carcinoma

Case number	*Age (years)*	*Sex*	*Type of tumour*	*Clinical state prior to ^{131}I therapy*	*Method of demonstrating ^{131}I concentration*	*Amount of ^{131}I given (mc.)*	*Improvement*		*Adjuvant therapy*	*State of patient*
							Clinical	*Radiological*		
R1	17	F	Papillary	Thyroid enlarged. Bilateral involvement of cervical glands	*In vivo* counting of cervical glands after removal of primary tumour	67	Complete resolution of enlarged glands	..	Partial thyroidectomy + 30mc. ^{131}I to induce hypothyroidism	Alive at 6 years
R2	56	M	Follicular	Numerous osseous metastases, many already treated with deep X-rays. Primary tumour removed 10 yrs. before	*In vivo* counting over metastases. Concentration found in some	100	None	None	..	Died at 2 years
R3	59	F	Follicular	Hyperthyroidism. Partial thyroidectomy revealed thyroid carcinoma	Concentration in tumour not certain, as normal thyroid tissue also present	25	Resolution of thyroid mass. Developed hypothyroidism	..	Deep X-ray therapy to thyroid	Alive at 9 months
R4	62	M	Follicular	Operation and deep X-rays to primary thyroid tumour 12 yrs. before. Then metastases in sternum, lungs, liver	*In vivo* counting. Concentration over sternum and left lung	90	None	None	..	Died at 9 months
R5	56	F	Follicular	Metastases in femur and vertebrae. Primary tumour mass in thyroid	*In vivo* counting over osseous metastases	310	None	Calcification and lack of growth of femoral lesion for 1 yr. No improvement of vertebral lesions	Thyroidectomy to induce hypothyroidism	Died at 3 years
R6	67	F	Follicular	Thyroidectomy and deep X-rays 7 yrs. before for hyperthyroidism and thyroid carcinoma. Then metastases in upper mediastinum and lungs	*In vivo* counting over upper mediastinum	93	Slight. Later developed femoral metastasis	Metastases in lungs cleared. Mediastinal mass smaller	..	Died at 18 months

The incidence of previous goitre should be taken as the minimal level, as an unknown number of those patients who are now dead were not questioned specifically about this point. Figures quoted in this respect have varied widely, and have usually been higher than in the present series. Harnett (1952) reported that 50 per cent. of patients gave a history of previous goitre, and 40 per cent. had had goitre for more than five years. In our series the proportion of male patients was smaller in the group with previous goitre (11 per cent.) than

TABLE X

Cases of Thyroid Carcinoma with Previous Goitre Compared by Age, Sex, and Survival to those without Previous Goitre

	Number of patients	*Male*	*Female*	*Mean age ± S.E. (years)*	*Duration of goitre*		*With histological evidence of thyroid carcinoma*	*Without histological evidence of thyroid carcinoma*	*Survival*		
					5–10 years	*> 10 years*			*Alive*	*Dead*	*Crude 5-year survival rate %*
No previous goitre	82	18	64	54·0 ±1·8	..	..	62	20	36	46	41
Previous goitre	18	2	16	53·7 ±3·6	3	15	16	2	8	10	44·5

in the group without goitre (22 per cent.), a finding which is to be expected from the known sex distribution of goitre (Table X). The mean ages of the groups with and without goitre are similar, but we have no information as to the age distribution of non-toxic goitre in the general population. The first symptoms in patients with previous goitre were similar to those found in the whole series: 14 (78 per cent.) complained of local symptoms referable to the neck. Nine complained of increase in size of their previous goitre, and the other five of pressure symptoms, such as dysphagia and dysphoea, or swelling of cervical lymph-glands. Two of the remaining four patients had hyperthyroidism, and symptoms referable to bony metastases were present in the other two cases. The incidence of the different types of carcinoma in this group with previous goitre was not strikingly different from that found in the non-goitrous group. Sixteen of the tumours were examined histologically, and papillary carcinoma (six cases) and follicular carcinoma (six cases) were commonest. There were four cases of undifferentiated carcinoma. McDermott, Morgan, Hamlin, and Cope (1954) found that the incidence of previous goitre was much higher in cases of follicular carcinoma. Similarly, the survival among this group did not differ significantly from that of patients without goitre. The crude five-year survival rate in the former group was 44·5 per cent. of nine cases, and in the latter it was 41 per cent. of 44 cases. This result is at variance with the series reported by Harnett (1952), in which five-year survival was much higher in the group with previous goitre, 53·2 per cent. as compared with 27·1 per cent.

Relation to Hyperthyroidism

There were seven cases (7 per cent.) of carcinoma with coexistent hyperthyroidism. Usually the rarity of coexistence of the two conditions is stressed

TABLE XI

Clinical and Pathological Features of Seven Cases of Coexistent Hyperthyroidism and Thyroid Carcinoma

			Criteria for diagnosis of hyperthyroidism			*Criteria for diagnosis of thyroid carcinoma*			
Case number	*Sex*	*Age (years)*	*Clinical features*	*4-hr. uptake (%)*	*48-hr. protein-bound activity (%/l.)*	*Histology of thyroid*	*Local invasion or recurrence*	*Metastases*	*Fate after diagnosis of carcinoma*
T1	F	53	Loss of weight, sweating, nervousness, and swelling of neck for 6 years. Hyperkinesis, tachycardia, and lid retraction. Thyroid enlarged, with hard mass in right lobe. Chest X-ray showed multiple rounded opacities at both lung bases	70	4·1	Follicular carcinoma	..	Pulmonary and vertebral, proved at autopsy	Died at 2·5 years
T2	F	60	Loss of weight, sweating, and palpitations for 1 yr. Tachycardia, tremor, and hyperkinesis. Smooth swelling in right lobe of thyroid. Hyperthyroidism treated with ^{131}I. Death 8 months later from cerebral metastases	67	1·55	Papillary carcinoma	..	Cerebral and pulmonary, proved at autopsy	Died at 0·75 year
T3	F	59	Nervousness, loss of weight, palpitations, and swelling of neck for 6 months. Hyperkinesis, tachycardia, and tremor. Smooth swelling in left lobe of thyroid. One year later dysphagia and stridor. Thyroid enlarged and hard	..	0·40	Follicular carcinoma	Invading neck-muscles at operation	..	Alive at 1 year
T4	F	56	Nervousness, loss of weight, and sweating, with swelling of neck for 5 months. Dysphagia for 2 months. Tremor, tachycardia, and large diffuse swelling of thyroid. Improved after two weeks on iodine, and operated on for hyperthyroidism	..	..	Undifferentiated carcinoma	Invading trachea and neck-muscles at operation	..	Alive at 1·8 years
T5	F	31	Loss of weight and swelling of neck for 1 year. Remained well for 2 years, after treatment with thiouracil for 5 months. Relapsed with nervousness, prominent eyes, and loss of weight. Tremor, tachycardia, and thyroid swelling, with glands on either side	..	0·41	Papillary carcinoma	..	Cervical lymph-glands, proved at operation	Alive at 2·9 years
T6	F	53	Goitre for at least 10 years. Nervousness, loss of weight, sweating, and increase in size of swelling. Hyperkinesis, tachycardia, and hard nodular swelling of thyroid. Operation was performed for dysphagia	62	1·35 but after partial removal of thyroid	Undifferentiated carcinoma	Invading neck-muscles at operation	..	Alive at 5·5 years
T7	F	60	Loss of weight, nervousness, and sweating, with swelling of neck for 2 years. Tremor, tachycardia, and firm enlargement of thyroid. Improved after 10 days on iodine, and operated on for hyperthyroidism	..	..	Follicular carcinoma	Recurrence in neck 2 years after operation	Mediastinal mass concentrating ^{131}I. Pulmonary opacities	Died at 7 years

(Means, 1948). The incidence in most reviews of thyroid carcinoma is low, but variable. Thus Pemberton (1939) reported an incidence of 1·3 per cent. in a total series of 774 cases, Ward (1944) 0·6 per cent. in 168 cases, Horn, Welty, Brooks, Rhoads, and Pendergrass (1947) 3 per cent. in 71 cases, and Clute and Warren (1935) 1·7 per cent. in 226 cases. On the other hand, Friedell (1941) found 13·8 per cent. in 412 cases, Cole, Slaughter, and Rossiter (1945) 13 per cent. in 38 cases, and Ward, Hendrick, and Chambers (1950) 26 per cent. in 112 cases. Similarly, Piercy (1956) found seven (12 per cent.) cases of carcinoma and toxic goitre in a total of 58 cases with carcinoma. Obvious reasons for these differences are the relatively small number of cases in each series, and the lack of uniformity, or even of any details, about the criteria for accepting the diagnosis of hyperthyroidism. In the present series the criteria for diagnosing hyperthyroidism have been strict. In five cases the clinical diagnosis was corroborated by radioiodine investigation. Otherwise clinical diagnosis was accepted only if there was obvious objective improvement with antithyroid medication, either by iodine or the thiouracil-like drugs. Thyrotoxicosis was suspected clinically in at least three other cases, but, as these criteria were not satisfied, they were not included in this group. Increase in basal metabolic rate was not accepted, as this may occur with any carcinoma. These seven cases also fulfilled rigid criteria for the diagnosis of carcinoma. They were all examined histologically, and all showed evidence of extension of tumour outside the thyroid, in the form of direct local invasion of surrounding structures or of lymphatic or haematogenous metastases.

The initial symptoms in all cases were due to hyperthyroidism, and had been present for periods varying from a few months to six years (Table XI). Carcinoma was obvious on the first examination in hospital only in Case T1, and this was principally due to finding multiple pulmonary opacities in the chest radiograph. Another patient (Case T6) had immediate operation for dysphagia, and there were grounds for a clinical diagnosis of carcinoma, as the thyroid swelling was very hard. The other five patients were all given medical or surgical treatment for hyperthyroidism, without any suspicion of the presence of a carcinoma. In the three patients treated surgically, tumour tissue was found at operation, and carcinoma confirmed histologically. Treatment of the other two was by thiouracil and radioiodine. In the patient treated with thiouracil carcinoma was diagnosed from the later development of cervical lymphatic metastases. The other patient (Case T2) was treated with ^{131}I for hyperthyroidism, and within three months her toxic symptoms were much improved. Six months after treatment she developed signs of cerebral metastases, and died two months later. At autopsy a papillary carcinoma of the thyroid was found, with cerebral and pulmonary metastases (Plate 23, Fig. 9). It is conceivable that the tumour developed only after treatment, but from analogy with the other cases it is probable that it was present when radioiodine was given. Thus, in five of the seven patients, carcinoma was not diagnosed when they were first seen in hospital. Three, however, had been referred to surgeons, and the diagnosis resulted from the selection of surgical treatment for the hyperthyroidism. If, as was possible,

they had been treated like the other two patients by medical means, the diagnosis of carcinoma would have been made only from the development of other manifestations.

In these seven cases of coexistent carcinoma and toxicity there was no association with any particular type of tumour. In three cases the predominant structure was follicular adenocarcinoma, and of the other patients two had a papillary carcinoma and two an undifferentiated solid growth. Black (1947) reported that, of 112 patients who had papillary adenocarcinoma, 15 per cent. had hyperthyroidism, which is a high incidence of such coexistence. An even higher incidence, of 36 per cent., was given by Chesky, Dreese, and Hellwig (1951) in a total of 25 cases with Hürthle-cell tumours.

Relationship to Previous Radiation

An attempt was made to find the incidence of exposure of the neck to ionizing radiation before the development of thyroid carcinoma. All the 46 patients who were alive at the end of 1955 were questioned about this point, and in addition the relatives of two patients, who had been under the age of 40 years when the diagnosis was made, and had died, were interrogated. The relatives of deceased patients who were over 40 years when diagnosed were not questioned, as it was unlikely that they could be certain about any previous radiation therapy. A history of any previous treatment by X-rays, radium, or any form of lamp treatment, to any part of the body was sought from patients and relatives. Details of any such therapy were then amplified from the hospital or clinic where this treatment had been given.

Eight patients were under the age of 35 years when thyroid carcinoma was diagnosed. Three of them had had previous therapy by ionizing radiation to the neck or neighbouring regions for various benign conditions. The first, a woman aged 33 years, was given X-ray treatment to her neck for eczema when she was 14 years and 17 years old. On each occasion the total dose was 300 r. by unfiltered X-rays of 75 kv. The anterior surface of the thyroid received approximately 240 r., and the dose to the thyroid tissue 2 cm. from its anterior surface was 120 r. The second, a man aged 25 years, had had radium treatment to a keloid of the right side of the neck, just above the thyroid cartilage, when he was 12 years and 13 years old. The following estimates of dosage appear reasonable from the known data about his treatment, and assuming average stature: about 6,500 r. were given to the keloid, and approximately 800 r. to the right lobe of the thyroid and 400 r. to the left. It is interesting that the initial symptom and sign of his thyroid carcinoma was swelling of the right thyroid lobe, with enlarged cervical glands on the right side. The third patient, a girl aged 12 years, had had radium treatment to a capillary naevus on her right mandible during a period of one year, beginning when she was only seven weeks old. Unfortunately some of the details of her treatment are missing, but again the following estimates appear reasonable, especially as the amount of radium and the duration of each treatment are known: approximately 400 r. were delivered to

the naevus, and the thyroid gland probably received between 60 and 120 r., assuming average stature.

None of the 40 patients who were over the age of 35 years when thyroid carcinoma was diagnosed had been treated by ionizing radiation at any time. Since, however, such treatment only became widespread in this country between 1930 and 1935, they would not have had the opportunity of receiving it for any condition occurring when they were young. With this reservation, the above findings suggest an association between exposure of the thyroid gland to ionizing radiation and the later development of carcinoma, but apparently only in the younger age-groups.

Discussion

There has been considerable discussion about the importance of previous hyperplasia in the development of thyroid carcinoma. The evidence for hyperplasia as a precancerous state is both clinical and experimental. It is a common belief that thyroid carcinoma develops more frequently in diffuse and nodular goitres. Three main points have been marshalled as evidence for the malignant potentialities of such glands. In most series of thyroid carcinoma a high incidence of previous thyroid enlargement, either diffuse or nodular, has been noted, but has varied widely in the different reports. Harnett (1952) described the incidence as 47·5 per cent., Horn, Welty, Brooks, Rhoads, and Pendergrass (1947) as 42 per cent., and Sloan (1954) as 24 per cent. In the present series 18 per cent. of patients had goitre for more than five years before the diagnosis of carcinoma was made. An immediate difficulty in the interpretation of these findings is the lack of knowledge regarding the prevalence of goitre in the population from which cases of thyroid cancer have been drawn. This information, unfortunately, is not available for any region. Hazard and Kaufman (1952), however, from 403 autopsies in adult patients, found 17 per cent. of thyroid glands to be over 35 gm. in weight, and half of these were nodular goitres. Crile (1953) has suggested that 10 per cent. of middle-aged women in the Great Lakes area of the United States have nodular goitres, and Sloan (1954) thought that the incidence in the general population might not be very different from that found in his cases of carcinoma. Weetch (1956) has examined 137 normal people, with no symptoms of thyroid disease, who were all resident in Sheffield. There were 26 men and 111 women, and the mean age was 45 years. He found that 10 per cent. had palpable diffuse enlargement of the thyroid. All those with thyroid enlargement were women, and they constituted 12·6 per cent. of the women examined. This incidence is not significantly different from the proportion of patients with previous goitre (18 per cent.) in the present series. The difficulty of interpretation, however, is shown by the series of 51 patients with thyroid carcinoma, who all had goitre, reported by Kearns, Davis, and Balkin (1955). We have already stressed the fact that many patients with carcinoma are subjected to operation for goitre with no clinical suspicion of malignancy, so that any patients then found to have carcinoma have had a previous goitre. A selection bias in favour of a high incidence will thus be present in any clinic where goitre is treated surgically. Thyroid carcinomas may enlarge

very slowly, and many of these previous goitres may have been carcinomatous from the beginning (Frazell and Foote, 1949). Sloan (1954) has emphasized the fact that most patients with thyroid carcinoma have no previous goitre. His report is most significant in this respect, since the non-malignant thyroid tissue was examined histologically, and the presence of diffuse or nodular goitre in 24 per cent. was confirmed. This is strong evidence against the belief that the majority of thyroid cancers arise in adenomatous goitres.

The importance of goitre in producing carcinoma has also been stressed by considering the incidence of carcinoma in diffuse and nodular goitres, though the published figures show considerable variation. Representative of such evidence are the incidences of 10·1 per cent. (Cope, Dobyns, Hamlin, and Hopkirk, 1949), 15·6 per cent. (Majarakis, Slaughter, and Cole, 1953), 17·1 per cent. (Cole, Majarakis, and Slaughter, 1949), 4·5 per cent. (Zimmerman, Wagner, Perlmutter, and Amromin, 1950), 12·5 per cent. (Hermanson, Gargill, and Lesses, 1952), 9·1 per cent. (Cattell and Colcock, 1953), 4·8 per cent. (Beahrs, Pemberton, and Black, 1951), 5·8 per cent. (Cloud and Branch, 1955), 7·6 per cent. (Hinton and Lord, 1945), and 5·4 per cent. (Horn, Welty, Brooks, Rhoads, and Pendergrass, 1947). A selection factor is obviously present, since all cases of goitre are not treated surgically, and these figures give no indication of the actual incidence of carcinoma in goitre. Sokal (1954) has attempted to assess the true incidence, and by very indirect estimates suggested that the risk of carcinoma developing in a goitre is only slightly higher than in a normal thyroid gland. Crile (1953) similarly considered that these high values are almost entirely explained by selection. Majarakis, Slaughter, and Cole (1953) and Cloud and Branch (1955) have pointed out that the large variation may be correlated with geographical regions, the proportion being higher where endemic goitre is present. The death-rate from thyroid carcinoma in Zürich has apparently fallen since the reduction of endemic goitre which followed the use of iodized salt (Wespi-Eggenberger, 1948). In other countries, however, endemic goitre has strikingly decreased without any apparent decrease in deaths from thyroid carcinoma (Zimmerman, Wagner, Perlmutter, and Amromin, 1950). This point is related to the other evidence that thyroid carcinoma is commoner in regions where endemic goitre is prevalent. Wegelin (1928) and Wynder (1952) have both produced evidence which suggests that this is so. Many observers have stressed the fact that carcinoma is commoner in goitre with a localized nodularity than in multinodular goitre (Cope, Dobyns, Hamlin, and Hopkirk, 1949; Majarakis, Slaughter, and Cole, 1953; Cole, Majarakis, and Slaughter, 1949; Hermanson, Gargill, and Lesses, 1952), though this difference was not found by Cloud and Branch (1955). The chance of developing carcinoma might be expected to increase with multiple nodules, so that the observed incidence would suggest some difference between solitary and multiple nodules. Thus it is possible that such solitary nodules are carcinomatous from the beginning. In interpreting these differences, however, it should be remembered that there is a striking lack of correlation between clinical estimation of thyroid nodularity and pathological findings (Mortensen, Woolner, and Bennett, 1955).

This variable, but high incidence of carcinoma in diffuse and nodular goitres has led to the view that operation should be done in all goitres. The difficulty in diagnosing carcinoma on clinical grounds from benign conditions of the thyroid gland gives further support to this opinion. Branson and Houston (1949) found 6·2 per cent. of carcinomas in 530 nodular goitres, and strongly advocated operative treatment. As has been shown, many cases of thyroid carcinoma are only recognized on surgical exploration of the gland or on later histological examination. Similarly, a review of all thyroidectomies performed during the last 10 years at Sheffield Royal Infirmary and Wharncliffe Hospital shows that there were 476 benign, non-toxic goitres, and 26 carcinomas (5·2 per cent. of the total). In 10 cases (2 per cent.) the diagnosis of carcinoma was not suspected before operation. It must again be emphasized, however, that these cases of goitre are not a representative sample of all goitres at risk. Selection is due to many causes, among which is the decision by the general practitioner to refer the patient to hospital. This is often done because of the possibility of malignant change. It is also important, in assessing the above incidences, to remember that the frequency of early carcinoma in clinically normal thyroid glands is not known and, as already shown, thyroid carcinoma most frequently arises in a normal gland. There is no doubt that in a certain number of patients with carcinoma the diagnosis is made earlier as a result of operation. On the other hand, the mortality after operation is about one per cent. (Branson and Houston, 1949), and the type of tumour present is probably a greater factor than early diagnosis in determining survival; this point is discussed later (page 230). Furthermore, in an area such as this, in which palpable abnormalities in the thyroid are common, particularly in older female patients, the number of operations would become exceedingly large. Accordingly, it is not our practice here to recommend operation indiscriminately in every case of goitre in anticipation of discovering a few otherwise unrecognized carcinomas at an early stage. In advising surgical removal or exploration other features are taken into consideration, such as the clinical condition of the goitre, the rate of growth of the nodules, and the liability to other complications, such as haemorrhage and tracheal compression.

Hyperplasia of the thyroid is most striking in hyperthyroidism, but the evidence that it is associated with an increased incidence of thyroid carcinoma is meagre. Cope, Dobyns, Hamlin, and Hopkirk (1949) found 0·8 per cent. of cases of thyroid cancer in patients with diffuse toxic goitre. Beahrs, Pemberton, and Black (1951) found 0·5 per cent. This incidence is doubled when hyperthyroidism occurs with nodular goitre (Cole, Majarakis, and Slaughter, 1949; Beahrs, Pemberton, and Black, 1951). Thus, compared with the results already quoted for goitre without hyperthyroidism, the incidence appears to be much lower when hyperthyroidism is present. As already mentioned, very variable figures have been reported as regards the incidence of hyperthyroidism in patients with thyroid carcinoma. It does not appear to be so rare as has been suggested (Means, 1948). In 7 per cent. of the present series there was reliable evidence of hyperthyroidism and carcinoma. Much of the variation may be explained by

lack of definite evidence to support the diagnosis of hyperthyroidism. Confirmation of such diagnosis by the basal metabolic rate (Friedell, 1941) is unreliable, as this rate may be raised in any type of malignant disease. In assessing the significance of the coincidence of these two conditions in 7 per cent. of the present series, there is one main selection factor which must be considered. Hospitals in the region, but outside Sheffield, only send patients with thyroid carcinoma to Sheffield Radiotherapy Centre if the tumour is likely to concentrate radioiodine. If the patient had coexistent thyrotoxicosis, radioiodine investigations would almost certainly be sought. In fact this condition applies only to Case T3 (R3), and the high incidence cannot be explained by this manner of selection. Selection due to Sheffield being a centre for the treatment of thyrotoxicosis by radioiodine must also be considered. Normally only patients over 45 years old are treated in this way, and thus more are likely to have coexistent carcinoma than would be found in the usual age distribution of patients treated for thyrotoxicosis. Only one patient, however, (Case T2) was referred for this purpose, and she was given radioiodine with no clinical suspicion of carcinoma at the time of treatment. Possibly thyrotoxicosis is commoner in the Sheffield region, as it is a known goitre area; this factor would inevitably increase the probability of the two conditions occurring together. A similar effect could result from an increased frequency of thyroid carcinoma in this region. Unfortunately the relevant information is not available.

There is strong evidence that the hyperthyroidism is only very rarely due directly to the production of thyroid hormone by the carcinoma. Cunningham, Hilton, and Pochin (1955) have found the iodine-concentrating activity of thyroid carcinomas to be usually less than 10 per cent. of that of normal thyroid tissue. Our experience, and that of others, is similar (Fitzgerald, 1955). Thus, even with the most differentiated thyroid tumours that have been investigated, about one kilogram of tumour tissue would be required to produce the average tenfold increase in thyroid-hormone production observed in hyperthyroidism. In only one of our patients was there evidence of such a large amount of tumour tissue, and this particular carcinoma did not concentrate radioiodine. The conclusion seems inescapable that the hyperthyroidism was due to excessive function of non-malignant thyroid tissue. A similar conclusion was reached by Berlin and Gargill (1947) in a review of the coexistence of diffuse toxic goitre and malignancy of the thyroid.

Experimental evidence of the tendency of hyperplastic thyroid glands to develop malignant tumours has been provided by producing chronic thyroid hyperplasia in several ways. As an analogy with the increased incidence of thyroid carcinoma in endemic goitre regions, Axelrad and Leblond (1953) have demonstrated the occurrence of thyroid carcinoma in rats maintained on an iodine-deficient diet. The tumours, however, could not be successfully transplanted. Prolonged administration of antithyroid agents, in particular thiouracil, has also been shown to produce thyroid carcinoma in rats (Purves and Griesbach, 1946; Money, Fitzgerald, Godwin, and Rawson, 1953). Metastasizing tumours occur only after administration of goitrogens for about 20 months,

which is half the lifetime of a rat. The development of such carcinomas is hastened by simultaneous administration of the carcinogen 2-acetylaminofluorene (Bielschowsky, 1944), and by radioiodine (Doniach, 1953). Successful transplantation of carcinoma from thiouracil administration in rats has been achieved by Purves, Griesbach, and Kennedy (1951). Thiouracil therapy for hyperthyroidism in man has not produced an increased incidence of thyroid carcinoma, and undue significance cannot be attributed to the development of thyroid cancer after only a few months of thiouracil administration, as described by Payne, Crane, and Price (1947).

The present series confirms the majority of previous reports concerning the biological characteristics of the different types of thyroid carcinoma. The three main types are papillary, follicular, and undifferentiated carcinoma. They show striking differences in incidence, sex ratio, age of onset, and survival. The type of tumour appears to be the main determining factor with respect to survival. As pointed out by many reports (Cunningham, Hilton, and Pochin, 1955; Hilton, 1956; Dobyns and Maloof, 1951; Rawson, Rall, and Robbins, 1953; Coliez, Tubiana, Dutreix, and Guelfi, 1953), the type of tumour is also the most important factor in determining successful treatment by radioiodine. The results of the present series are fully in agreement with this view, and in fact only one girl, with a papillary carcinoma which was forming colloid, has apparently been cured by radioiodine therapy.

The potentialities of ionizing radiation in producing malignant disease are well known, and have resulted in restriction of the use of radioiodine therapy for hyperthyroidism. In most centres only patients over 45 years old are treated. If thyroid carcinoma is induced by radioiodine it is likely that it will have the usual latent period of many years, which has been found in the case of malignant disease produced in other sites by ionizing radiation, such as skin cancer and leukaemia (Medical Research Council, 1956). There has been no age restriction in the use of radioiodine for diagnostic purposes, as only small quantities of radiation are delivered to the thyroid gland with the doses commonly used. There have, however, been recent reports (Duffy and Fitzgerald, 1950; Simpson, Hempelmann, and Fuller, 1955; Clark, 1955) which suggest an association, in the younger age-groups, between thyroid carcinoma and previous exposure of the neck region to relatively small doses of ionizing radiation. The present series confirms these findings to some extent, as three of the eight patients who were under the age of 35 years when thyroid carcinoma was diagnosed had been given treatment by ionizing radiation for various conditions. The period between exposure to radiation and development of thyroid carcinoma was 12 years, 16 years, and 13 years. There is no evidence so far that the use of radioiodine, either for diagnosis or for therapy, has led to the development of thyroid carcinoma (Lindsay, Dailey, and Jones, 1954; Blomfield, Jones, Macgregor, Miller, Wayne, and Weetch, 1955), but an association with acute leukaemia has been suggested in patients who have been treated for hyperthyroidism (Pochin, Myant, and Corbett, 1956; Abbatt, Farran, and Greene, 1956), or treated for thyroid carcinoma with much larger doses of ^{131}I (Seidlin, Siegel, Melamed, and Yalow,

1955; Blom, Querido, and Leeksma, 1955). From the evidence available, however, it appears that an association between thyroid carcinoma and previous radiation is found only in the younger age-groups. There is also experimental evidence that radioiodine may produce thyroid carcinoma. Goldberg and Chaikoff (1952) induced both carcinomas and adenomas in rats 12 to 18 months after a single dose of 400 μc. of ^{131}I. Such a dose delivers at least 100,000 r. to the rat's thyroid gland. No such effect has been noted with smaller amounts of radiation, which would be comparable to a radiation dose of 10,000 r. given for treatment of hyperthyroidism. Doniach (1953), as already mentioned, found that 30 μc. of ^{131}I hastened the development of thyroid carcinoma in rats treated with methyl thiouracil. There is a striking species difference, however, for thyroid carcinoma has not been induced in mice by ^{131}I (Gorbman, 1949).

Radioiodine has been widely used in medical practice for less than 10 years. If it is comparable with external radiation, sufficient time may not have elapsed for a higher incidence of thyroid carcinoma to become evident. The difficulties in establishing the diagnosis, and the uncertainty regarding other possible aetiological factors, show that it will not be easy to determine the influence of radioiodine on the development of thyroid carcinoma in the older age-groups even after the lapse of the necessary interval of time.

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Summary

1. One hundred cases of thyroid carcinoma have been reviewed. The patients were seen at a radiotherapy centre in a region where goitre is common.

2. The difficulties in establishing a clinical diagnosis of carcinoma before the development of metastases have been stressed. In many cases carcinoma was diagnosed only after direct inspection of the gland at operation and histological examination.

3. Survival is closely related to the histological type of tumour, which is the major factor in determining the prognosis. Concentration of radioiodine by tumour tissue occurred in only seven cases.

4. The association between the presence of a simple goitre and the subsequent development of a carcinoma is reviewed. The majority of thyroid carcinomas do not arise in adenomatous goitres.

5. In seven cases of carcinoma there was coexistent hyperthyroidism. In one

case carcinoma was diagnosed six months after ^{131}I treatment of the thyrotoxicosis.

6. In three out of eight patients who developed a carcinoma before the age of 35 years there was a history of ionizing radiation to the neck in childhood, and the dose given to the thyroid gland has been calculated. In the older patients there was no evidence of previous radiotherapy.

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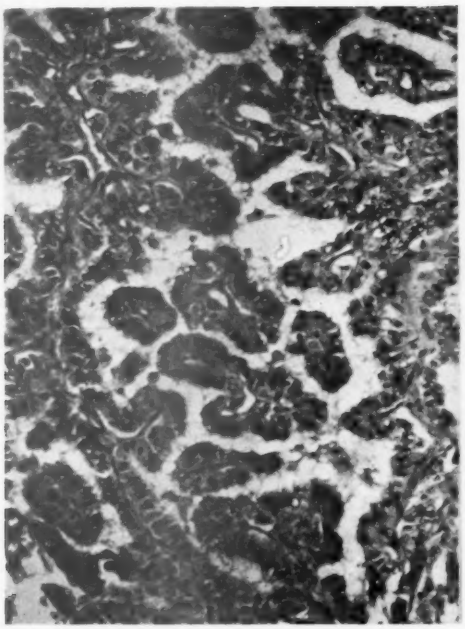

FIG. 2. Papillary carcinoma without colloid formation, coexistent with hyperthyroidism (haematoxylin and eosin, × 170)

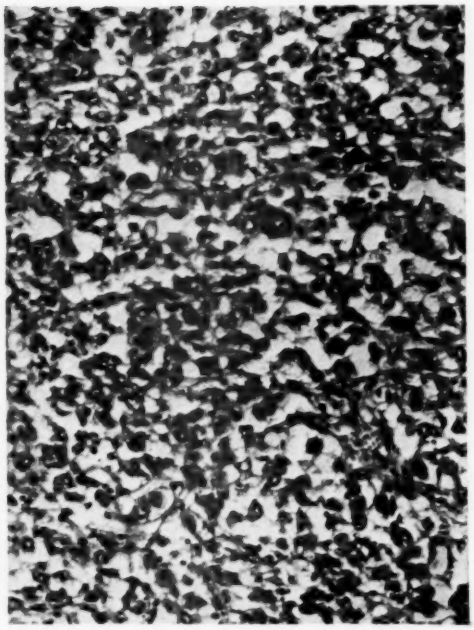

FIG. 3. Undifferentiated carcinoma (haematoxylin and eosin, × 170)

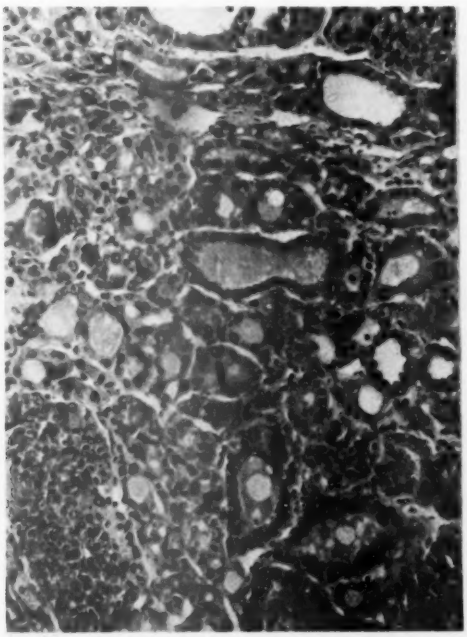

FIG. 4. Follicular carcinoma with well-developed follicles and solid alveoli. This carcinoma was coexistent with hyperthyroidism (haematoxylin and eosin, × 170)

FIG. 5. Metastasis of follicular carcinoma in femur. The thyroid tissue is indistinguishable morphologically from normal thyroid (haematoxylin and eosin, × 170)

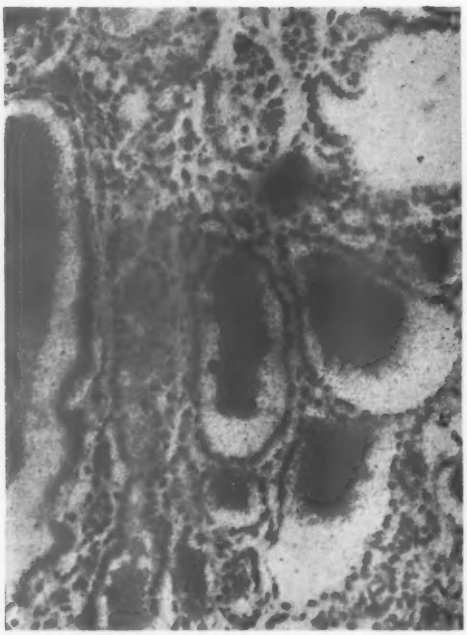

FIG. 6. Autoradiograph of papillary carcinoma, 48 hours after administration of ^{131}I. There is some colloid formation, and obvious but irregular concentration of radioactivity (pre-stained with haematoxylin, × 170)

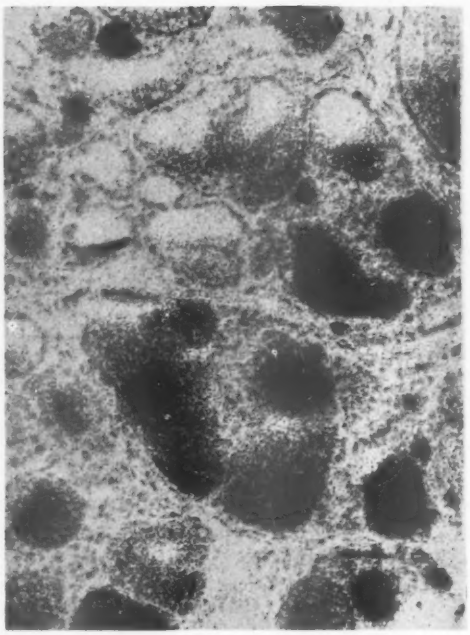

FIG. 7. Autoradiograph of follicular carcinoma with irregular concentration in the follicles (pre-stained with haematoxylin, × 170)

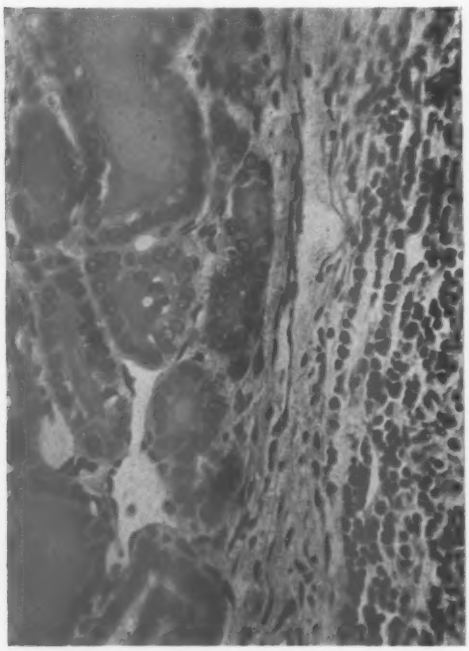

FIG. 8. Metastasis of papillary carcinoma with colloid formation in a cervical lymph-gland (haematoxylin and eosin, × 300)

FIG. 9. Metastasis of papillary carcinoma in lung, coexistent with hyperthyroidism (haematoxylin and eosin, × 170)

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RECURRENT APHTHOUS ULCERATION OF THE MOUTH[1]

A Study of the Natural History, Aetiology, and Treatment

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With Plate 24

Greek ἄφθαι, mouth ulcers; ἅπτειν, to set on fire.

The first use of the term *aphthai* in relation to disorders of the mouth is credited to Hippocrates (460–370 B.C.), though it is likely that he used it in describing the lesions of thrush. In his treatise on *Diseases and Surgical Operations of the Mouth* (1778), Jourdain-Berchillet discusses aphthae in considerable detail, but is clearly again describing cases of thrush. The first valid clinical description of the chronic recurrent form of the disease appeared in 1888 (von Mikulicz and Kümmel); and Sibley (1899) provided a description in English. Despite numerous publications in the last 50 years, each mainly devoted to a description of a few cases, the existence of 12 synonyms for the disorder emphasizes our lack of knowledge of the nature and variations of this disease:

Acute aphthous stomatitis.
Vesicular stomatitis.
Maculofibrinous stomatitis.
Recurrent aphthous stomatitis.
Canker sore.
Dyspeptic ulcers.
Habitual solitary aphthous ulcer.
Mikulicz's aphthae.
Periadenitis mucosa necrotica recurrens.
Ulcus neuroticum mucosae oris.
Ulcus necroticum mucosae oris.
Fragmentary Behcet symptom-complex.

Sibley's first description in English concerned three women, and the relationship of the disorder to financial stress in each case prompted the title of 'ulcus neuroticum mucosae oris'. The familial character of the disease was stressed by Löblowitz (1910) in describing its occurrence in a father and seven of his children. Strandberg (1918) reported eight cases in one family, and Pappworth (1941) six cases in one family.

That the buccal lesions were associated with similar ulceration elsewhere was

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noted by Strandberg (1918) in a patient with concomitant scrotal ulcers, and by Fordyce (1920) and Ravell (1932), whose patients had lesions in the mouth and on the vulva; Whitwell (1934 *a*, *b*) described involvement of the mouth, genitals, eye, and skin, and Hunt (1934) of the mouth, genitals, and skin. In 1937 Behcet described the same combination of symptoms. Since Behcet's paper the symptom-complex, in the complete and in fragmentary form, has been reported by many authors (Curth, 1946; Bechgaard, 1940; Jensen, 1944), and the disorders of recurrent ulceration of the mouth, with or without genital involvement, have become interwoven with the triad of Behcet. In the review by Touraine (1941) three clinical groups emerge from a consideration of 274 reported cases of aphthous-like ulcerations. The first group consists of ulcers involving only the mucosa of the mouth or genitalia, or both; the second consists of ulcers upon the mucosa of the mouth and the skin of the genitalia, and the last of ulcers of the mouth associated with generalized lesions of the skin, and occasionally of the eyes and joints. In his review there are 130 cases of ulceration confined to the vulva, and 23 cases confined to the penis. The mouth and genitalia were involved together in 104 cases, and the mouth and skin in 56. Eye lesions occurred together with buccal lesions in 16 cases, and joint lesions in 14. An association between recurrent aphthous ulceration of the mouth and other, notably gastro-intestinal, diseases has been reported. A relation with ulcerative colitis has been selected by some authors (Jensen, 1944; Brooke, 1953; Todd, 1954); with ileitis by Bechgaard (1940); and with idiopathic steatorrhoea by Cooke (1953). The incidence of the disorder in the general population, however, is such that its reported presence in one or a few cases of other diseases is of little significance.

Ignorance of the nature of the disease is reflected in the varying fashions of aetiology, and in the remarkable diversity of therapeutic specifics offered during the past 50 years. A viral aetiology has been supported by many authors (Scott, Steigman, and Convey, 1941; Woodburne, 1941; Cahn, 1950; Robinson, 1950; Kilbourne and Horsfall, 1951), and denied by Touraine (1941) and Frech (1945). Usually the virus of herpes simplex has been indicated (*Journal of the American Medical Association*, 1949), but this possibility appears to have been excluded by the careful studies of Scott, Steigman, and Convey (1941), Blank, Burgoon, Coriell, and Scott (1950), and Dodd and Ruchman (1950). Faure (1953), and Sédallian, Garin, and Faure (1954) have reported finding objects looking like toxoplasma in aphthous stomatitis. The *Bacillus crassus* had a long and mainly European vogue, being held responsible by Lipschütz (1923), McDonagh (1924), Carol and Ruys (1928), Samek and Fischer (1929), Kumer (1930), and Matras (1932). Allergy to chocolate (Alvarez, 1937) and allergy to hormones (Zondek and Bromberg, 1947) have been suggested causes. The range of therapeutic measures recommended has been summarized on various occasions (*Journal of the American Medical Association*, 1949; *British Medical Journal*, 1948), and has included repeated vaccinations, vitamins A, B, C, D, and E, oestrogens and androgens, sulphonamides, antibiotics, local applications of gentian violet, and deep X-rays. Internal arsenic was highly recommended by Jadassohn (Epstein, 1930), and aureomycin by Distelheim and Sulzberger (1949), Everett (1950), and

Fisher and Leider (1951). The use of cortisone has been reported in a single case and not found to be effective (Alphonse, Jadassohn, and Paillard, 1952). Radiotherapy was reported as highly successful by Harrison (1953). Numerous histological studies have always revealed entirely non-specific changes of an inflammatory or degenerative nature (Frech, 1945; Prinz and Greenbaum, 1939), or with secondary necrosis overlying an arteriolitis of the deeper vessels in the area (Touraine, 1941). The object of the present study is to examine the incidence of the disorder, define its natural history, and investigate critically the aetiology and treatment.

Methods

1. *Establishing the incidence.* One thousand patients consecutively attending the medical and surgical out-patients' clinics of the Royal Infirmary, Sheffield, were asked to fill in a questionnaire with the aid of a trained receptionist. All those who admitted to having had the disorder were then referred to the authors, and, with the assistance of coloured photographs and clinical examination, the diagnosis was confirmed or refuted. Because it was possible that the incidence may be atypical in the highly industrial and predominantly working-class population attending the Sheffield clinics, the same procedure was repeated at all the surgical, medical, paediatric, and gynaecological clinics of the Western General Hospital in Edinburgh, which serves a much more mixed population, with a fair proportion of the merchant and professional classes. Five hundred and eighty seven patients were questioned in this second inquiry. Finally, 151 patients consecutively attending the surgery of a general practitioner were examined in the same way.

2. *The aetiology and natural history.* We have been able to study 120 cases of recurrent aphthous ulceration of the mouth referred to us by general practitioners, and by colleagues on the staffs of the Royal Infirmary, Sheffield, and the Western General Hospital and Royal Infirmary of Edinburgh. In each case a detailed standard form was completed, from which the data for analysis were acquired. Fourteen patients in whom the disability was severe were admitted to the wards for detailed investigation, which included gastroscopy, sigmoidoscopy, a gastric function test, a three-day fat-balance study, and uropepsinogen excretion. Barium-meal studies, biopsy, and trauma tests were carried out in a few cases. Fifty-five patients were interviewed in one or more sessions of three hours each by one of the authors (J. K.), and a careful psychiatric assessment was made of the patient and of the history of the disorder in each case. By a few intelligent female patients diaries relating the incidence of the lesions to the menses were carefully maintained for six months or more. All patients were followed up, at intervals of usually one month, for six months, and many have been followed up for over two years. In a few patients in remission, and in two of the authors susceptible to the disorder, attempts were made to provoke the appearance of lesions by intramucosal injections of saline and histamine, and by trauma to the mucosal surface of the mouth.

Virus investigations were made in co-operation with Professor C. H. Stuart-Harris. Complement fixation tests for the herpes simplex virus were made on from two to four specimens of blood, removed at intervals of one to six months, from 42 patients who had recurrent aphthous ulceration, and on blood from 72 control subjects chosen at random from a mixed normal population. Blood was also tested from 15 patients with proved recurrent herpes simplex, and

TABLE I

The Incidence of Aphthous Ulceration

Sex and status	*Number of patients*	*Aphthous ulceration*		
		Positive history	%	*Sex-ratio in adults*
A. *Sheffield Royal Infirmary:*				
Adult male	490	75	15·3	1M:1·33F
Adult female	510	103	20·2	
Total	1,000	178	17·8	
B. *Edinburgh Western General Hospital:*				
Adult male	220	45	20·4	
Adult female	310	84	27·0	1M:1·35F
Children under 10 years	57	12	21·0	
Total	587	141	24·0	
C. *General practice:*				
Adult male	44	3	6·8	
Adult female	91	11	12·8	1M:1·8F
Children under 10 years	16	2	12·5	
Total	151	16	10·6	

from eight patients with chronic ulceration of the mouth not of herpetic or aphthous origin. The same sera were also examined by Professor C. P. Beattie for toxoplasma antibodies by a complement fixation test (Sabin and Feldman, 1949). Samples of faeces and saliva, and scrapings from ulcers in the mouth, were taken from five patients with recurrent aphthous ulceration who were found to have no history of herpes, and whose serum was negative to complement fixation tests for herpes simplex, and attempts were made to grow virus from inoculation of these materials on to chick egg membrane.

3. *Assessment of treatment.* Fifty patients were subjected to single and double 'blind' therapeutic trials. The value of folic acid, nicotinic acid, riboflavin, vitamin-B complex ('becosym'), ethisterone, cortisone, local aureomycin, and radiotherapy was investigated. Where the treatment was oral, dummy tablets of lactose and citrate were prepared, and the patient was given two separate courses, of one month's duration each, of the dummy tablets, and one month's course of the specific preparation under investigation. Each series of courses was given in random order. All patients were seen at least once monthly. In the radiotherapy group neither the authors nor the patients were aware which patients had been exposed to X-rays; patients sent for radiotherapy were treated at random by the therapist, the beam in approximately half of the cases being screened off from the patient, who otherwise went through the same procedure as those exposed. At the completion of the follow-up the therapist revealed which of the patients had in fact been treated.

Results

The Incidence

The overall incidence for all ages and both sexes in the 1,738 patients questioned was 335 (19·3 per cent.). The details are shown in Table I. If the small group from general practice is excluded, the overall incidence in 1,587 patients remains 20·1 per cent. That is, at some period in their lives one in five of the population suffers from recurrent aphthous ulceration of the mouth. Approximately one

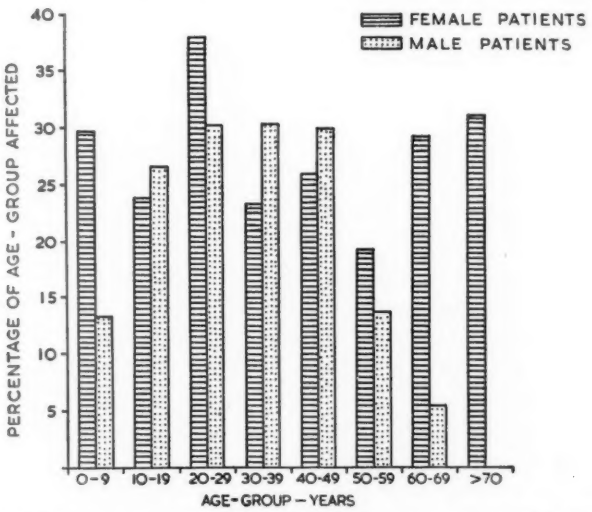

FIG. 1. The incidence of aphthous ulceration related to age and sex in 337 female and 250 male patients.

in four female subjects (1:4·3) and one in six male subjects (1:5·9) appear thus to be affected. The incidence of the disorder according to the age and sex of the patients in the Edinburgh survey illustrates the discrepancy between the sexes over 49 years of age (Fig. 1).

Studies of 120 Cases of Recurrent Ulceration

Age at attendance for treatment. The majority of the 120 patients (65 per cent.) were between 20 and 49 years of age, with an even distribution of attendances in each of the third, fourth, and fifth decades. There were exactly twice as many women as men in the series, but this is partly a reflection of the greater ease with which women could attend the surgery and clinics. Notably, however, the series contained 22 women, but only three men, between the ages of 50 and 69 years. This difference of 7·3:1, compared with the general distribution for all age-groups of 2:1, and the disorder incidence of 1·5:1, is significant.

Age at onset. The highest incidence of onset in both sexes was in the second decade, and in over 50 per cent. of patients the onset occurred between the ages of 10 and 30 years. In 10 per cent. of the female patients the first attack occurred

between the ages of 50 and 59 years, whereas no ulcers began in men of that age-group. Whereas from 10 to 19 years the relative incidence in male and female patients was almost two to one, from 20 to 29 years the ratio was reversed. In nearly half of the male patients the disorder began between the ages of 10 and 19 years; in female patients it first appeared between the ages of 10 and 30, and thereafter the age at onset was approximately the same as in men until the menopausal years were reached (Fig. 2).

The frequency of attacks. There appears to be a rhythmical periodicity in the

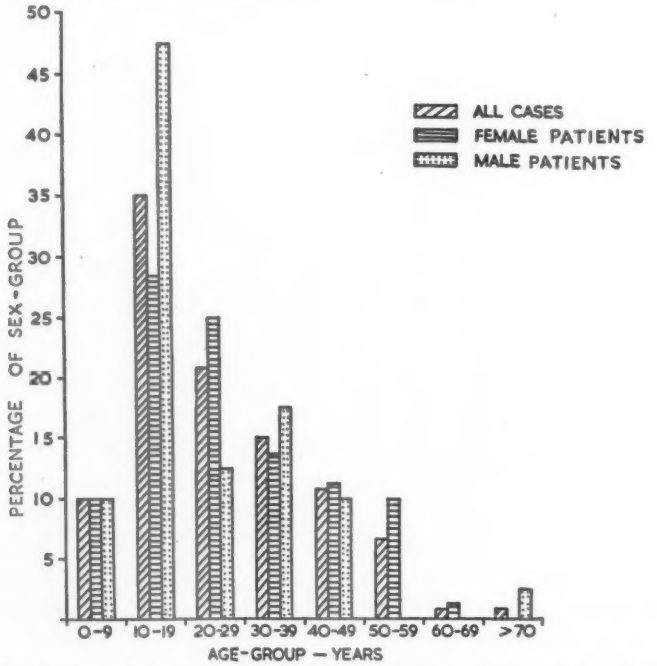

FIG. 2. The relation between sex and age at onset of aphthous ulceration in 80 female and 40 male patients.

attacks in most subjects, but a sharp difference occurs between the sexes in the relative frequency of attacks. Nearly 40 per cent. of female patients suffer crops of ulcers at intervals of less than eight weeks, and usually with intervals of less than a month. Most male patients, however, (45 per cent.) experience new crops at three- to four-month intervals (that is, usually about four times a year), or else are never without ulcers in the mouth. A much higher proportion of male than female patients (17·5 per cent. as against 3 per cent.) show no periodicity, with wholly irregular intervals between attacks (Table II).

The duration of the disorder. No significant difference appears between the sexes in respect of the length of time the recurrent disorder has persisted. Between 65 per cent. and 70 per cent. of the patients of either sex had had the disorder from one to 14 years, and 30 per cent. from 15 to 40 years or more.

The hereditary aspects. Fifty-five of the 120 patients gave a family history of the disorder (45·8 per cent.). In 22 of these 55 cases (18·3 per cent.) one or both parents were known to be affected, in 18 cases (15 per cent.) one or more siblings, in 21 cases (17·5 per cent.) one or more children, and in five cases (4·1 per cent.) the consort. Only seven cases occurred in which more than three members of the

TABLE II

The Relation of Periodicity to Sex

Periodicity	*Number of cases*	%	*Female patients*		*Male patients*	
			Number	%	*Number*	%
Continuous	22	18·3	12	15·0	10	25·0
Less than 4 weeks	26	21·7	24	30·0	2	5·0
4–7 weeks	22	18·3	17	21·2	5	12·5
8–11 weeks	9	7·5	6	7·5	3	7·5
12–15 weeks	19	15·8	9	11·2	10	25·0
More than 15 weeks	12	10·0	9	11·2	3	7·5
Wholly irregular	10	8·3	3	3·7	7	17·5
Total	120	..	80	..	40	..

family were affected. It seems clear from the very low incidence in the consorts that the familial incidence is not based on contact infection. In several cases in which the children were affected anticipation appears to have occurred, the disorder appearing in the child at an earlier age than it did in the parent. The youngest child with the disorder seen in a familial relationship was 11 months old. Both the mother and father were sufferers, the mother since five years of age, and the father since adolescence. The overall percentage of a familial relationship among the 120 patients seems too low, in relation to the high incidence of the disease, to suggest that factors of inheritance play more than a minor part in aetiology.

Factors precipitating attacks. A useful and definite statement could be obtained from only 90 of the patients (60 female and 30 male subjects). The outstanding feature, indicated by 21 per cent. of the patients, was a preceding period of mental stress associated with domestic, including financial or sexual, problems in marriage. Local trauma seemed to play a part in some cases, but in the majority nothing definite of this nature had been observed by the patients, even after a lifetime with the disease. Local trauma included dental manipulations, and soreness after eating nuts or toast and after pipe- or cigarette-smoking. The occurrence of the initial attack within a few days of the death of a loved one (usually a parent or child) was noted in eight cases in female patients, and only once in a male patient. In many cases the loss was sudden and unexpected, and caused acute stress to the relatives.

The location of the lesions. The mucosa of the buccal cavity was involved in all but three of the 120 cases. The sites of election were the inside of the cheeks opposite to the molar teeth in the upper jaw, and inside the upper and lower lips. The upper and lower sulci were also commonly involved. Ulcers appeared elsewhere as follows: the tongue (85 cases); the fauces and pharynx (58 cases); the mucosal surfaces of the vulva and vagina (12 cases); the mucosal surfaces of

the eyes (two cases); the urethra (one case); the skin of the scrotum (one case). Thus 12 of 80 female patients (15 per cent.) had periodic involvement of the vulva or vagina in the course of their disorder, whereas the genitalia were involved in only two male patients.

Associated disorders in 120 cases. A history of dyspepsia was found in 37 cases (30·8 per cent.): investigation disclosed that a peptic ulcer could be proved in 11 instances (9 per cent. of the 120), and the other 26 were, by their clinical nature and on radiological investigation, considered to be functional in type. Thus the incidence of peptic ulcer in this group of cases is not higher than would be expected from an investigation of any population of 120 subjects of similar ages. Steatorrhoea was found in one case, and a distal proctocolitis of moderate degree in another. Recurrent urticaria was recorded in five cases, and other skin diseases, mainly acne vulgaris, psoriasis, and chronic eczema, in a further 20 (17 per cent. of 120). No other disorders of significance were recorded.

In-patient studies. Fourteen patients, seven of each sex, with more severe recurrent or continuous ulceration, were admitted to the wards, and the following investigations were made:

Gastroscopy (12 cases). The mucosa was found to be normal in seven cases, atrophic in two, and hypertrophic in two; in the remaining patient a gastric ulcer was present. *Sigmoidoscopy* (12 cases). The appearance was normal in 11 cases; in one patient a moderate degree of proctocolitis was present, but with no evidence of aphthous ulceration. *Gastric function tests.* A histamine-response test was performed on 12 subjects, and the output of free acid was found to be normal in six cases, slightly reduced in five, and high in one case. Uropepsinogen excretion was measured in 12 subjects, and was within the normal range in all. Fat-excretion was studied with a three-day balance test, on the basis of an intake of 50 gm. in 24 hours. The mean excretion in 10 cases was 4·2 gm., with a range of 1·2 to 9·7 gm. This limit of 9·7 gm., which represents a moderate steatorrhoea, was found in a boy of 12 years, who showed an abnormal skeletal and mental development, and undoubtedly had coeliac disease which had been overlooked.

An attempt to produce ulceration was made on four patients, and simultaneously on the two authors who were susceptible to the disorder. At separate sites on the mucosa lining the lower lip an intramucosal injection of 0·1 ml. of normal saline, and 0·1 mg. (in 0·1 ml.) of histamine acid phosphate, was made through a fine hypodermic needle, raising a bleb. An aphthous ulcer appeared in only one subject at the site of injection, and this was at the point where saline was injected.

The Relation of Ulceration to Mental Illness and Stress

The complete data will be published elsewhere by one of us (J. K.), and only an outline of the findings is reported here. The patients were carefully surveyed by both the physicians and the psychiatrist, and a joint discussion of each case took place in an attempt to reduce bias to the minimum. Nevertheless, evidence

emerged of a close association between life experiences, individual personality, and *recurrent* ulceration, especially where the disorder was severe. Of 55 cases closely investigated, established mental illness was recognizable in 18 instances (33 per cent.). The diagnoses included chronic anxiety state, hysteria, obsessional state, hypochondriasis, paranoia, and epilepsy. The percentages of male and female patients affected were similar (31 per cent. of male and 35 per cent. of female patients). All but two of the patients appeared to be of average or superior intelligence. The tendency to neurosis was widespread in the remainder. Of the whole group, 71 per cent. were anxious, 51 per cent. experienced notable depressed moods, 38 per cent. showed hypochondriacal preoccupations, and 35 per cent. showed obsessional features. Almost all (89 per cent. of the group) had a life pattern characterized by conformity and good behaviour. Hard work, striving, neatness and orderliness were recognized in 71 per cent. Regular church attendance was claimed by 40 per cent. Fully half had become socially isolated. Only one patient took alcohol regularly, and 73 per cent. were non-smokers. A history of an unfavourable early environment was obtained in the majority (71 per cent.). There was evidence of ill-adjusted parents in 42 per cent., and of chronic alcoholism in the father in 27 per cent.; 60 per cent. had been reared in conditions of poverty.

Severe environmental or emotional stress immediately preceded the onset of ulceration in 63 per cent. of the female and 59 per cent. of the male patients. In nine of the 55 patients (eight female and one male) ulcers appeared soon after the death of a parent or child, and in nine other patients (five female and four male) at the development of marital failure with sexual frigidity in the consort. A close relationship between stress and recurrent attacks was found in half of the female and one-third of the male patients. Episodes of marital maladjustment appeared responsible in eight cases, and stresses of social environment in 12 cases.

Therapeutic Trials

Fifty patients in whom ulceration was either continuous, or recurrent at least once in four weeks, were subjected to controlled therapeutic measures. Twenty-three patients were divided into four groups; all were given courses of dummy tablets for one month, after which the respective groups were given folic acid 5 mg. thrice daily, nicotinamide 50 mg. thrice daily, riboflavine 5 mg thrice daily, and two tablets of 'becosym' for a month thrice daily. Finally all four groups resumed dummy tablets for a third and final month. No significant change in the progress of the disease was found in any of these cases. Three patients with severe continuous ulceration followed a similar controlled régime and were given cortisone, 25 mg. thrice daily for one month, without effect, and a fourth patient was given 25 mg. twice daily for three months with no effect. Three women who suffered from regular premenstrual aphthae took ethisterone, 50 mg. daily, for a fortnight before menstruation during the active-test month of a controlled test, with no effect on the ulceration. Seventeen patients were

treated by radiotherapy to the buccal mucosa at the Sheffield Radiotherapy Centre. The 'double blind' technique was used; the patients were seen monthly for three to six months after treatment. Of nine who were found to have had active radiotherapy, one had a complete remission lasting three months, and one a partial remission; the remaining seven patients were not helped. Eight patients had been used as controls, and one had a remission lasting four months; no change occurred in the remaining seven.

Local application of aureomycin. A therapeutic measure which appeared to influence the disease was the application of a suspension of aureomycin (250 mg. in 10 ml. of water). Eleven patients, who had been treated with other drugs without success, used this paint three times daily. They found no change in the number or frequency of the ulcers, but the duration of ulcers was reduced, usually from 10 to five days, and each application had an analgesic effect lasting from half an hour to two hours. Only one patient failed to obtain any relief.

Cortisone administration in acute attacks. A severe relapse in a case of resistant multiple buccal ulceration was treated with 1·2 gm. of cortisone, given in six days; by the end of the course all lesions in the mouth had healed, without residual scarring. The patient was admitted to hospital for the treatment.

Studies of a Virus Aetiology

1. *Comparison with cases of recurrent herpes simplex.* All 92 cases of recurrent herpes seen during the last five years were analysed. The sex incidence of this disorder was found to be equal, and unlike that of recurrent aphthous ulceration.

The distribution of age on attendance was different from that of aphthous ulceration in the following respects: first, nearly one-quarter of the patients were under 10 years of age. Secondly, the maximum incidence appeared in the age-group of 10 to 19 years, compared with 20 to 49 years in cases of aphthous ulceration. In the 10-to-19 years age-group there was a larger attendance of female patients, whereas in the case of aphthous ulceration male patients predominated in this group.

The distribution of age at onset. The age at onset was known with certainty in only 70 of the 92 cases of recurrent herpes. The greatest incidence was in the age-group 0 to nine years, 80 per cent. of the first attacks occurring at under 19 years; in cases of aphthous ulcer the greatest incidence was in the group of 10 to 19 years, and nearly all the initial attacks occurred at between 10 and 39 years. First attacks appearing in the menopausal age-group were seen in only 3 per cent. of cases of recurrent herpes, compared with 21 per cent. of cases of recurrent aphthous ulceration.

The duration of recurrent herpes was known from the records of 70 patients. Only 12 had had lesions appearing for more than nine years, compared with 56 of 120 patients with recurrent aphthous ulceration. In over 50 per cent., when they were seen, the duration was less than four years.

2. *The complement fixation test for herpes.*

(1) *Comparison of aphthous ulcer cases and controls.* In a preliminary study

in the laboratory of Professor C. H. Stuart-Harris, using a single antigen, the results appeared to suggest marked similarity between cases of recurrent herpes and cases of aphthous ulcers (Table III). Subsequent studies, however, were made in the same cases, utilizing three different testing antigens, and it then appeared that two components exist in the antigens, a sedimental (virus particle) material, and a non-sedimental (soluble) material. Human sera may possess antibody for

TABLE III

Results of the Complement Fixation Tests for Herpes Virus, using a Single Antigen

Case group	*Number tested*	*Positive fixation*	*Negative fixation*
A. (1) *All cases irrespective of history of herpes:*			
Aphthous ulcers	42	25* (59·5%)	17 (40·5%)
Controls	72	25* (34·7%)	47 (65·3%)
* $\chi^2 = 6{\cdot}63$, $n = 1$, $P = 0{\cdot}01$ (Significant)			
(2) *Cases with negative history of herpes:*			
Aphthous ulcers	19	10† (52·7%)	9 (47·3%)
Controls	38	10† (26·0%)	28 (74·0%)
† $\chi^2 = 10{\cdot}3$, $n = 1$, $P = 0{\cdot}001$			
(3) *Cases with positive history of herpes:*			
Aphthous ulcers	23	14 (60·9%)	9 (39·1%)
Controls	34	15 (44·2%)	19 (55·8%)
B. *15 Cases of recurrent herpes simplex:* Positive fixation in 9 (60%), negative in 6. Cf. aphthous ulcers, all cases (59·5%).			
C. *8 cases of ulcerated mouth not due to herpes or aphthae:* Positive fixation in 1, negative in 7.			

one component and lack it for the other. The full details of this study are reported elsewhere (Balducci, Stuart-Harris, and Tyrrell, 1956), and only a relevant part is noted here. The three antigens were prepared with egg-membrane, mouse brain, and rabbit kidney; the results in sera from cases of recurrent herpes were all positive with mouse brain, and half were positive with the other antigens. Similar results were found in the control cases with a positive history of herpes, but a consistently lower proportion of positive results occurred in control cases with a negative history of herpes. The sera from the aphthous cases showed results similar to those in the controls. When mouse-brain antigen was used, only two of six cases of aphthous ulceration with no history of herpes had a positive titre, whereas all four of the aphthous cases with a positive history of herpes had a positive titre (Table IV). Thus, in tests using mouse-brain antigen, the evidence of herpes infection is clearly negative in cases of recurrent aphthous ulceration, but always positive in cases of recurrent herpes. These results may explain the erroneous conclusions of previous workers who found that aphthous ulceration was a clinical variant of herpes virus infection.

(2) *Comparison of aphthous ulcer and control cases according to age-group.* Of the patients tested for complement fixation, the ages were known in 42 cases of

aphthous ulceration and 33 control cases:

	Number	*Fixation test positive*
Aphthous ulcer: all patients under 40 years	21	13
Controls: all patients under 40 years	19	8
Aphthous ulcer: all patients over 40 years	21	12
Controls: all patients over 40 years	14	2

Compare the proportion of positive results in the whole group: 25 out of 72 control cases, and 25 out of 42 cases of aphthous ulceration (Table III).

TABLE IV

Results of the Complement Fixation Tests for Herpes Virus, using Three Different Antigens

		Titre results with antigens from					
		Mouse brain		*Kidney*		*Chorion-allantois*	
Subjects	*Number*	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*
1. *Controls:*	22	..	..	..	..	..	..
Positive history of herpes	12	1	11	5	7	8	4
Negative history of herpes	10	5	5	8	2	7	3
2. *Recurrent herpes:*	14	0	14	7	7	6	8
3. *Aphthous ulceration:*							
Positive history of herpes	4	0	4	4	9	6	7
Negative history of herpes	6	4	2				

3. *Attempts to grow virus.* No growth on chick egg membrane occurred after inoculation with ulcer scrapings, saliva, and faeces, from any of the five patients with recurrent aphthous ulceration in whom the history and serological evidence of herpes infection was negative.

4. *Toxoplasma complement fixation.* Antibodies were not found more frequently in the patients' sera tested than in the controls. The only serum which gave a significant result was from a control subject.

Comment

It is clear that recurrent aphthous ulceration of the mouth is a disorder of common incidence and the cause of considerable disability, and therefore deserving of more than the scant attention devoted to it in the textbooks of medicine. In the male sex the disorder tends to burn out after middle age, and few cases are seen in men over 50, whereas in women this reduction of incidence is not observed. This difference is almost entirely due to the occurrence of first attacks in the menopausal age-group. That there may be important endocrine factors in the resistance of the individual to mucosal ulceration of this kind is suggested not only by this menopausal group of cases, but also by the observation, repeated and confirmed in several of our female patients, though not in all,

that the ulcers tended to disappear entirely throughout pregnancy, only to return in the post-partum period. Similar metabolic factors may underlie the greater frequency of appearance of new lesions in female patients, and the considerably greater tendency in women to a rhythmical periodicity of attacks, over 50 per cent. of women having lesions every third to eighth week, though with no traceable relationship to the menses.

The present study has failed to provide any definite evidence regarding aetiology. The complete failure to grow the virus from severe cases, the results of the antigen studies, and the sharp differences in the natural history of the disorder from that of recurrent herpes simplex, make it distinguishable from a variant of that disease. The striking similarity between cases of recurrent herpes simplex and cases of aphthous ulcer in the first group of complement fixation tests, in which a single antigen was used, taken in conjunction with the results of the comparison between aphthous ulcer cases and controls over and under 40 years, suggests that the antigen response to herpes normally dies out with advancing age, but that in the presence of aphthous ulcers or recurrent vesicular herpes the response is maintained. It seems possible that complement fixation, in cases of recurrent aphthous ulcer, represents either a non-specific continued stimulation of antigen by mouth ulcers, or an anamnestic reaction to antigen from another virus. Against a virus origin, however, are the results of tests using mouse-brain antigen, the complete lack of evidence of direct transfer, and the strong familial tendency. The overwhelming association seen so often in our subjects between mental stress, psychopathological disturbance, and the onset and fluctuations of the disease, underlines these factors as the main aggravating or precipitating mechanisms, though not the cause, of the disease. Since over 20 per cent. of patients suffered from a psychosomatic dyspepsia, it might seem that the alimentary tract is specially vulnerable in these subjects, but this view was not borne out by endoscopic examination or studies of function. The normal output of acid and uropepsinogen also disposes of the possibility of over-activity of the adrenals, or of the autonomic nervous system, being a factor in the disorder. According to Cooke (1953) almost 100 per cent. of patients with steatorrhoea have aphthous ulcers, but only a single case of steatorrhoea was observed in the present series. Most illuminating, if distressing, was the complete failure of all modes of treatment, with the exception of the relative relief afforded by aureomycin, and the astonishing effect sometimes seen as the result of suggestion alone.

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Summary

1. Published accounts of the aetiology, natural history, and treatment of recurrent aphthous ulceration of the mouth are reviewed.

2. The incidence of the disorder in the general population has been investigated. An overall high incidence, with a sex difference, is described.

3. A detailed study of the social and psychological background, the natural history, and the clinical features of the disorder in 120 subjects is presented. The data are compared with those resulting from a simultaneous study on 92 cases of recurrent herpes simplex.

4. An extensive serological and virological study of the aetiology is described, and the results analysed.

5. Therapeutic trials of many agents, using single and 'double blind' methods, are reported and assessed.

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FIG. 3. A typical example of the small recurrent aphthous ulcer.

FIG. 4. Recurrent aphthous ulceration of the lip. A moderate-sized lesion, showing the well-defined though sinuous outline and characteristic areola of hyperaemia.

FIG. 5. Severe aphthous ulceration in the mouth, in the position opposite the upper molar teeth where it is most commonly seen, showing the considerable reaction in the surrounding tissue. This appearance is sometimes referred as due to possible malignancy.

FIG. 6. Giant aphthous ulceration of the buccal mucosa complicating a severe case of ulcerative colitis.

FIG. 7. Multiple aphthous ulceration of the tongue appearing in the subject illustrated in Fig. 4, but on a different occasion.

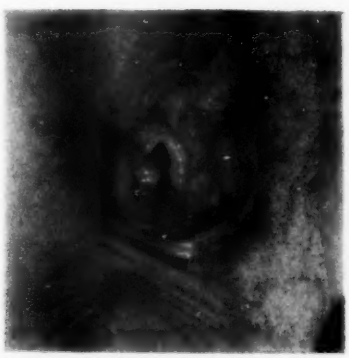

FIG. 8. A typical example of an aphthous ulcer at the vaginal introitus in a young subject with severe recurrent mouth lesions.

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THE TREATMENT OF HAEMOCHROMATOSIS[1]

With particular reference to the Removal of Iron from the Body by Repeated Venesection

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With Plates 25 and 26

In haemochromatosis there is extensive deposition throughout the body of iron in the form of haemosiderin. The aetiology is unknown in most cases (idiopathic haemochromatosis), but the condition can occur in chronic refractory anaemia, where the deposition of iron is due to multiple blood transfusions and coincident oral and intravenous iron therapy (exogenous or transfusion haemochromatosis) (Kark, 1937; Schwartz and Blumenthal, 1948; Muirhead, Crass, Jones, and Hill, 1949; Wallerstein and Robbins, 1953; Wyatt, 1956). Haemochromatosis has also been described in Bantu natives suffering from malnutrition associated with an excessive dietary intake of iron (cytosiderosis) (Gillman, Mandelstam, and Gillman, 1945; Gillman and Gillman, 1945; Walker and Arvidsson, 1950). The present paper is concerned only with the idiopathic form of the disease.

The heaviest concentrations of iron in haemochromatosis occur in the liver and pancreas; next to these, the organs most severely affected are usually the thyroid, anterior pituitary, and heart (Sheldon, 1935). Fibrosis is associated with these iron deposits, invariably in the liver, and frequently in the pancreas, thyroid, and heart. The main clinical effects of the disease are cirrhosis of the liver, diabetes mellitus, hypogonadism, and congestive cardiac failure. Asthenia and pigmentation of the skin are also common manifestations. Once symptoms have become sufficiently severe to call for medical advice, progressive deterioration commonly occurs. Within a few years death usually results from damage to the liver, pancreas, or heart (hepatic failure, oesophageal haemorrhage, primary carcinoma of the liver, diabetes and its complications, or myocardial failure). Less commonly death is due to intercurrent infection, such as pneumonia or tuberculosis. Sheldon (1935), on the basis of 311 cases, estimated that death occurred on an average 18½ months after diagnosis, the most common cause being diabetic coma (50 per cent.). Insulin, however, had not been available for most of the diabetic patients included in his series. Finch and Finch (1955), in a comprehensive survey of reports published since 1935 (787 cases), found the average expectation of life to be 4·4 years from the onset of symptoms, although very occasional patients had been reported to live for 20 to 30 years. In their series the complications of cirrhosis of the liver caused nearly 45 per cent. of

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deaths, and heart failure caused approximately 30 per cent. The death-rate from diabetic coma had fallen to less than 5 per cent. In patients with diabetes the average length of life from the onset of the diabetes, even when insulin was available, was only three years. When heart failure followed involvement of the myocardium, death usually resulted within one year of the onset of failure.

It is generally believed that the excessive iron deposits in haemochromatosis in some way cause cell damage, with subsequent fibrosis and malfunction of the affected organs (Beyers and Gitlow, 1951; Finch and Finch, 1955). On this hypothesis treatment in recent years has been directed towards reducing the iron stores, with the object of improving the function of the organs and arresting the progress of the disease (Finch, Haskins, and Finch, 1950; Davis and Arrowsmith, 1952). The present paper describes the treatment of six male patients with haemochromatosis, and deals particularly with the reduction of the iron stores by repeated venesection.

The Theory of Iron Metabolism, and its Application to Treatment in Haemochromatosis

The mechanism of intestinal absorption of iron is not known with any certainty. The available dietary iron is initially in the ionic state, or released from organic combination by digestive enzymes. It is absorbed better as the ferrous than the ferric ion, although non-ionized but soluble iron complexes may also be absorbed (Finch and Finch, 1955). The presence of hydrochloric acid in the gastric juice is not now considered to be essential for the absorptive process (Brummer, 1950; Moore and Dubach, 1951). Phosphates, and other substances which form insoluble iron complexes, may diminish iron absorption (Hegsted, Finch, and Kinney, 1949). Iron may be absorbed from any part of the small intestine, but under normal conditions is mainly absorbed from the duodenum. An average diet contains 10 to 25 mg. of iron daily, and in a normal subject only a small proportion (less than 10 per cent.) of this amount is absorbed (Sharpe, Peacock, Cooke, and Harris, 1950; Chodos, Ross, Apt, Halkett, and Pollycove, 1954). In acute loading experiments with oral iron salts there is a limit to the amount of iron that may be absorbed, the percentage absorption falling rapidly as the amount given is increased (Granick, 1946). To explain this limitation of iron absorption the existence of a 'mucosal block' has been inferred, in which the rate of passage of iron across the mucosal cell is restricted by the limited availability of the intracellular proteins which transport it, and in which the passage can be in one direction only (Granick, 1949, 1954). In the presence of anaemia absorption is increased (Balfour, Hahn, Bale, Pommerenke, and Whipple, 1942; Chodos, Ross, Adams, and O'Brien, 1952), and the degree of increase appears to be related to the iron-content of the erythron rather than to the total iron stores in the body (Haskins, Stevens, Finch, and Finch, 1952). Once iron has passed the unidirectional intestinal barrier it remains within the body, except for a very small amount, usually less than 1 mg. per day, which is lost in urine, faeces, and desquamated skin (McCance and Widdowson, 1937, 1938–9, 1943; Barer and

Fowler, 1937–8; Adams, Leslie, and Levin, 1950). In women there is an additional loss during menstruation of 10 to 40 mg. per month (Ohlson and Daum, 1935). The total iron in the body of a normal subject is 3 to 5 gm. (Finch and Finch, 1955). Red-cell haemoglobin contains 1·5 to 3 gm.; storage iron, present in the tissues as ferritin and haemosiderin, accounts for 1 to 1·5 gm. (the liver contains 300 mg.); the remainder occurs in the plasma as transferrin (iron in combination with a β_1-globulin), and in tissue iron complexes such as myoglobin, cytochrome, and catalase.

In haemochromatosis it is believed that there is an inborn error of metabolism in the intestinal mucosal cells, which results in a slightly increased absorption of iron of the order of 3 to 5 mg. per day throughout life (Granick, 1949). The excretion is not increased by a corresponding amount, and the surplus iron is deposited in the tissues as granules of haemosiderin. By middle age the amount of iron absorbed and stored has become massive, from 20 to 50 gm., and the associated damage to organs produces symptoms. The liver alone may contain up to 39 gm. (Sheldon, 1935). In women haemochromatosis is infrequent, and develops at a later age, probably because of a protective loss of iron through menstruation and pregnancies. The aim of treatment in haemochromatosis is to minimize iron absorption from the gut and, more important, to reduce existing stores to a normal level. Experimentally, a low-iron and high-phosphate diet can lessen the absorption of iron in rats (Hegsted, Finch, and Kinney, 1949). In cases of haemochromatosis, however, it is impossible to maintain an effective low-iron diet (less than the absorption rate of 3 to 5 mg. per day), and the administration of phosphates has not been found to reduce the absorption of iron (Bothwell, van Doorn-Wittkampf, du Preez, and Alper, 1953). As ferric salts are absorbed less readily than ferrous salts (Moore, Dubach, Minnich, and Roberts, 1944), an aluminium hydroxide gel was used by Davis and Arrowsmith (1953) with the object of keeping dietary iron in ferric form, but no measure of its effect was made. Excretion of iron in the urine can be increased by the use of various intravenous chelating agents (Wishinsky, Weinberg, Prévost, Burgin, and Miller, 1953; Figueroa, Adams, Bassett, Rosove, and Davis, 1954), and by intramuscular dimercaprol (Ohlsson, Kullendorff, and Ljungberg, 1953); but the amount excreted rises only to 4 to 10 mg. per day, and excretion by this route is therefore too small to be of practical value. Iron can be extracted from the body very effectively by venesection, however, as every 500 ml. of blood removed contains approximately 250 mg. of iron. In haemochromatosis the haemosiderin in the abnormal iron deposits is readily available for haemoglobin synthesis (Beyers and Gitlow, 1951), and repeated bleeding is therefore a very good method of reducing these stores.

Methods

The diagnosis of haemochromatosis was established in all cases by liver biopsy: in four by needle puncture, and in two at laparotomy. The haematological state and the function of organs mainly affected (liver, pancreas, thyroid,

and heart) were studied before treatment commenced. A diet containing 100 gm. of protein and approximately 7 mg. of iron was taken daily by all patients. No vitamin supplements were prescribed. Insulin was given for the diabetes in Cases 1 and 2, and *l*-thyroxine for the hypothyroidism in Case 1. The congestive cardiac failure in Case 6 was treated by orthodox methods. Testosterone therapy was refused by the patients with hypogonadism. A phosphate mixture (potassium dihydrogen phosphate 20 gr. and disodium hydrogen phosphate 30 gr.) was given before meals, in view of the theoretical possibility that it could diminish iron absorption, and calcium (lactate or gluconate 15 gr.) was given between meals to combat any associated interference with calcium absorption, particularly as osteoporosis may occur in haemochromatosis and was already present in Cases 2 and 6.

Removal of 500 ml. of blood by venesection once every week was planned for each patient. Direct venepuncture in the antecubital fossa or forearm was performed with a standard blood-taking set, local anaesthesia being required by only three patients. The veins were used regularly for two, three, or four years without difficulty, and blood was removed without reinfusion of separated plasma. Throughout the course of treatment the patients carried on with their normal work, and attended hospital for venesection during off-duty periods. In Cases 1 and 6 the weekly venesection had to be reduced to 350 ml., as the removal of larger volumes produced a feeling of tiredness in Case 1 and faintness in Case 6. Regular venesection was continued until eventually a moderate anaemia developed (haemoglobin 10 to 11 gm. per 100 ml.).

Throughout the course of treatment frequent observations were made on the clinical state, body-weight, blood picture, and serum-protein values. The level of serum-iron was estimated at intervals by a method described in the Appendix. Various tests of organ function were repeated a number of times during treatment and after its completion. Liver biopsy was repeated at the end of treatment in five of the patients. After completing the course of venesection follow-up studies were made in order to show whether, and when, maintenance venesection was required.

Results

General. Before treatment all the patients complained of general weakness and fatigue. By the end of the course of venesection these symptoms had disappeared, and a full day's work could be done without tiring by every patient but one. One patient (Case 4), a chronic hypochondriac, was the least improved symptomatically, but nevertheless needed fewer days off work than in previous years. In Cases 5 and 6 the body-weight increased by 7 kg.; in the other cases it was unchanged. Skin pigmentation, which was present originally in every patient, disappeared completely in Cases 1 and 4, and appreciably diminished in the remainder. The scanty and female type of body-hair in Cases 2, 3, and 6 was, however, unaltered. In Cases 1, 2, 5, and 6 libido was lost or reduced; it returned to normal only in Case 1. The decalcification shown in the X-rays of the skeleton of Cases 2 and 6 was unchanged at the end of treatment.

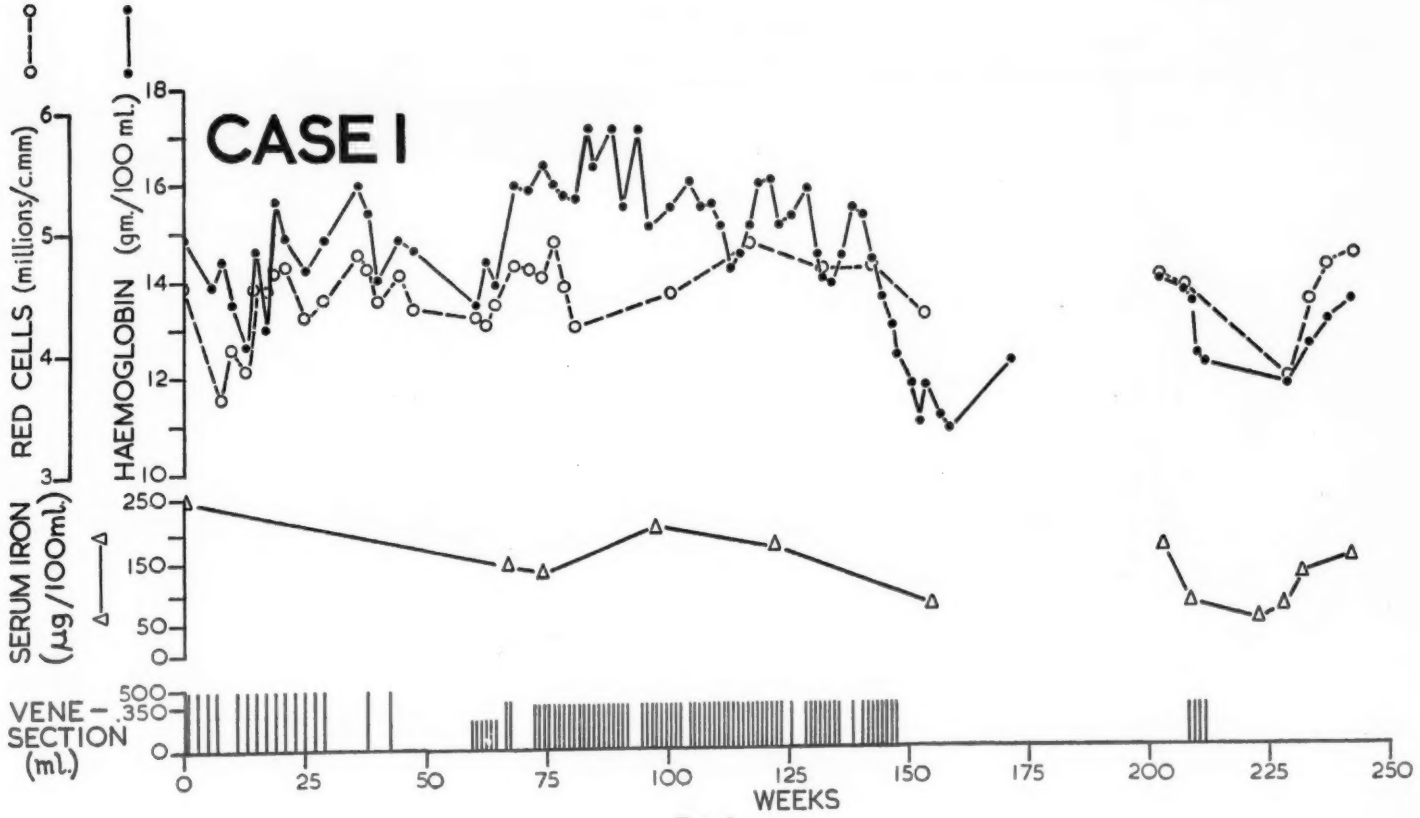

FIG. 1.

FIGS. 1 to 6: The haematological response to treatment by repeated venesection in Cases 1 to 6.

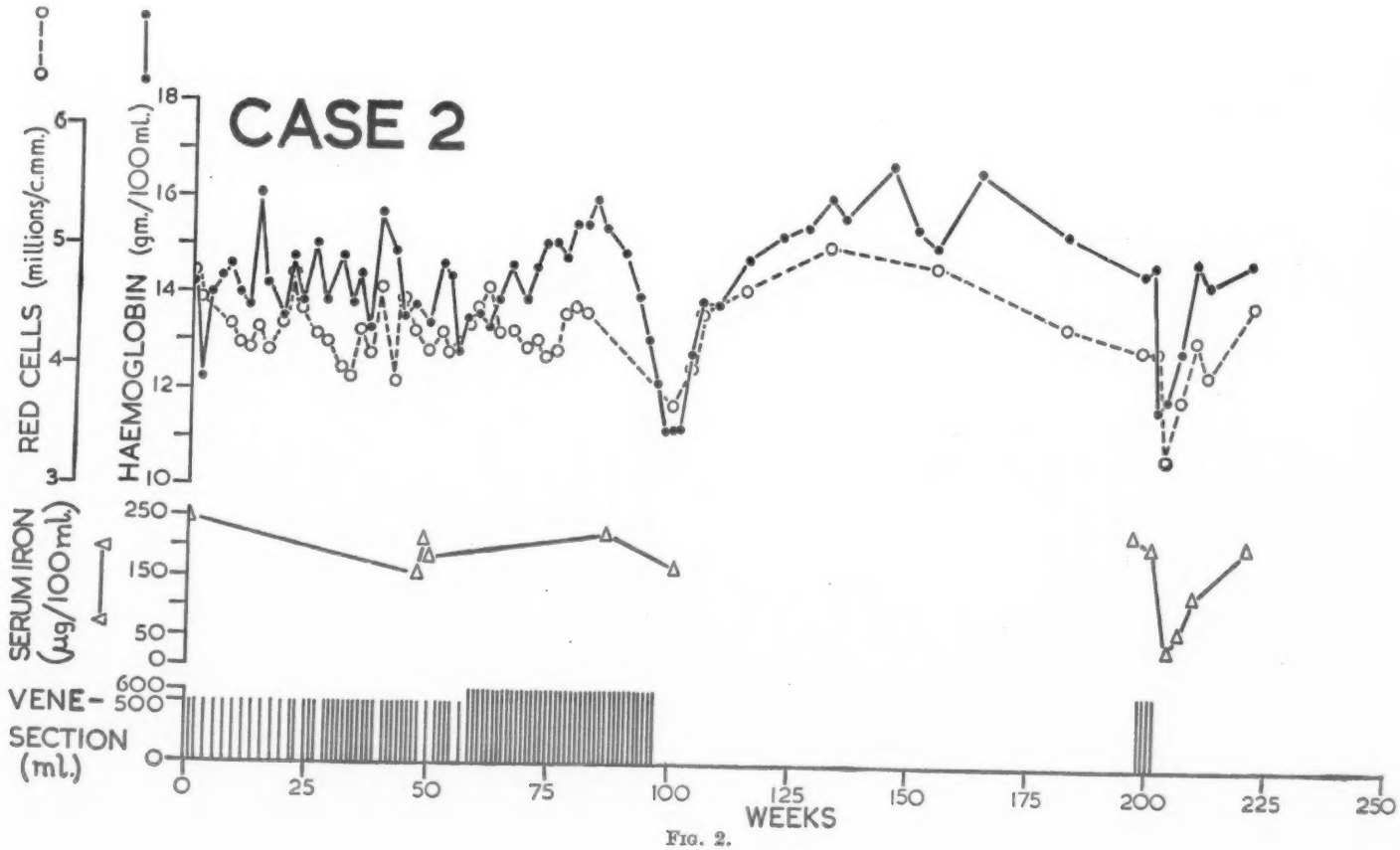
CASE 2
RED CELLS (millions/c.mm.)
HAEMOGLOBIN (gm./100 mL.)
SERUM IRON (µg/100 mL.)
VENE-SECTION (ml.)
WEEKS
0
25
50
75
100
125
150
175
200
225
250

FIG. 2.

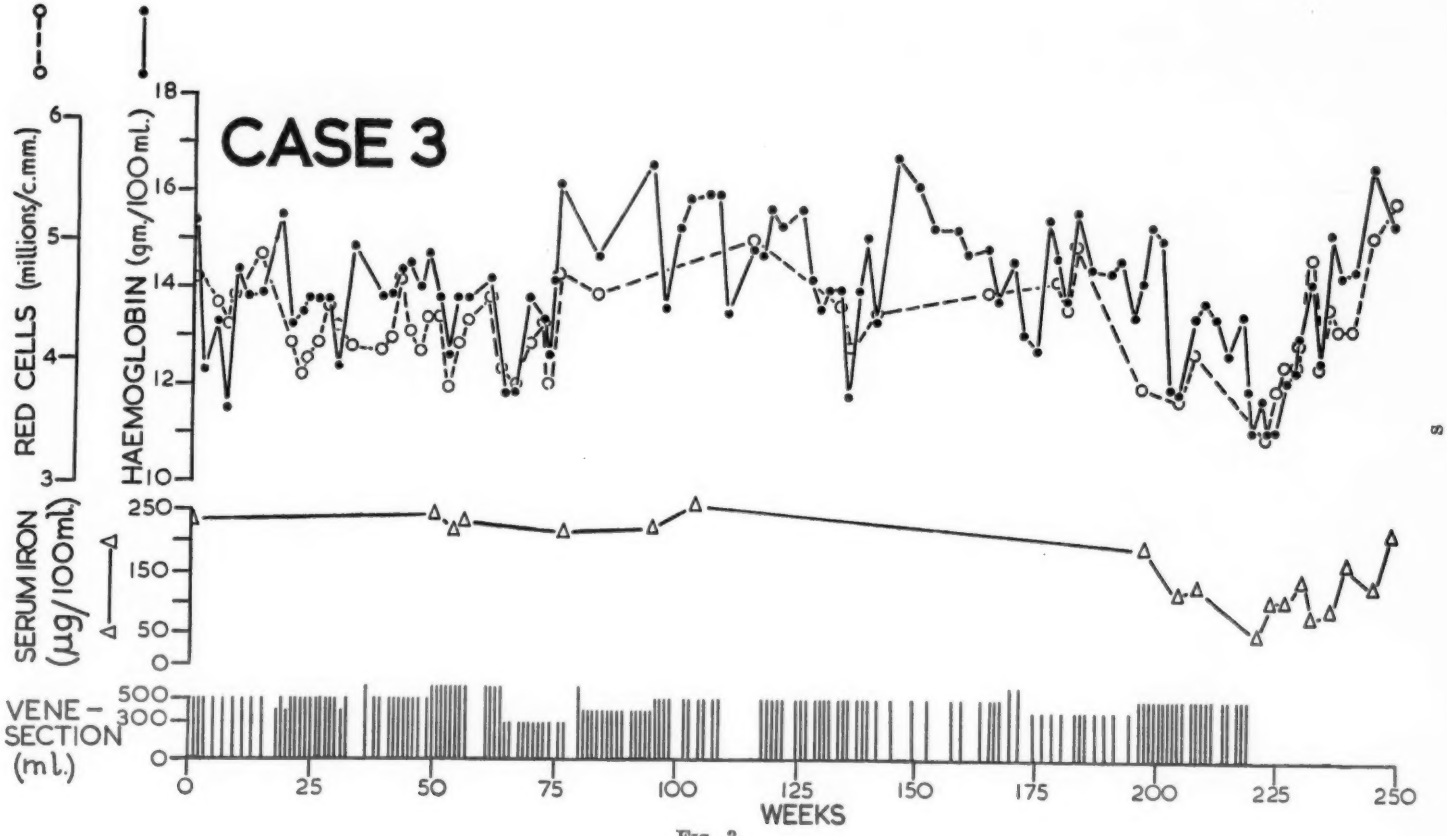
CASE 3
RED CELLS (millions/c.mm.)
HAEMOGLOBIN (gm./100 mL.)
SERUM IRON (µg/100ml)
VENE-SECTION (ml.)
WEEKS
0
25
50
75
100
125
150
175
200
225
250

FIG. 3.

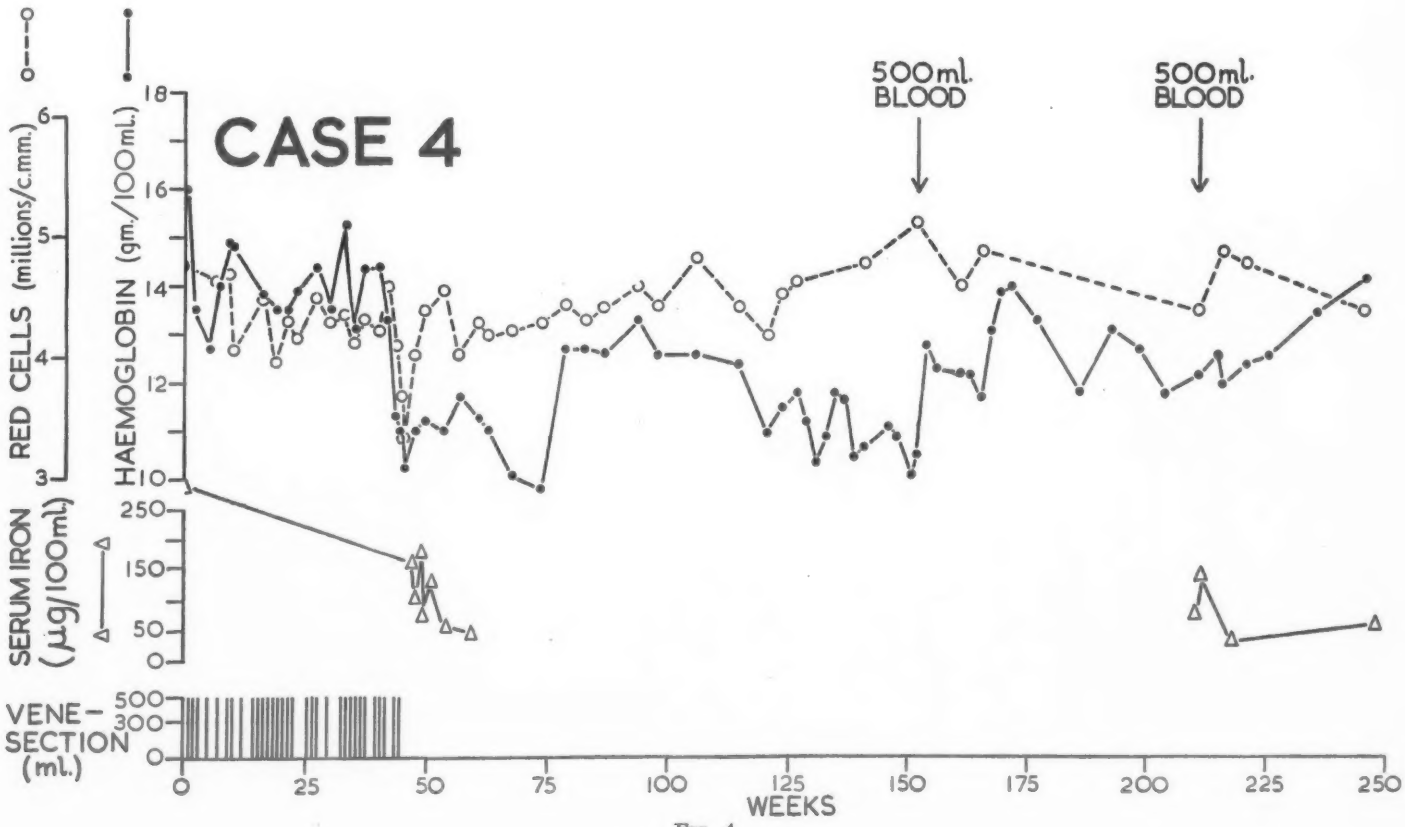
CASE 4
500ml. BLOOD
500ml. BLOOD
RED CELLS (millions/c.mm.)
HAEMOGLOBIN (gm./100ml.)
SERUM IRON (µg/100ml.)
VENE-SECTION (ml.)
WEEKS

FIG. 4.

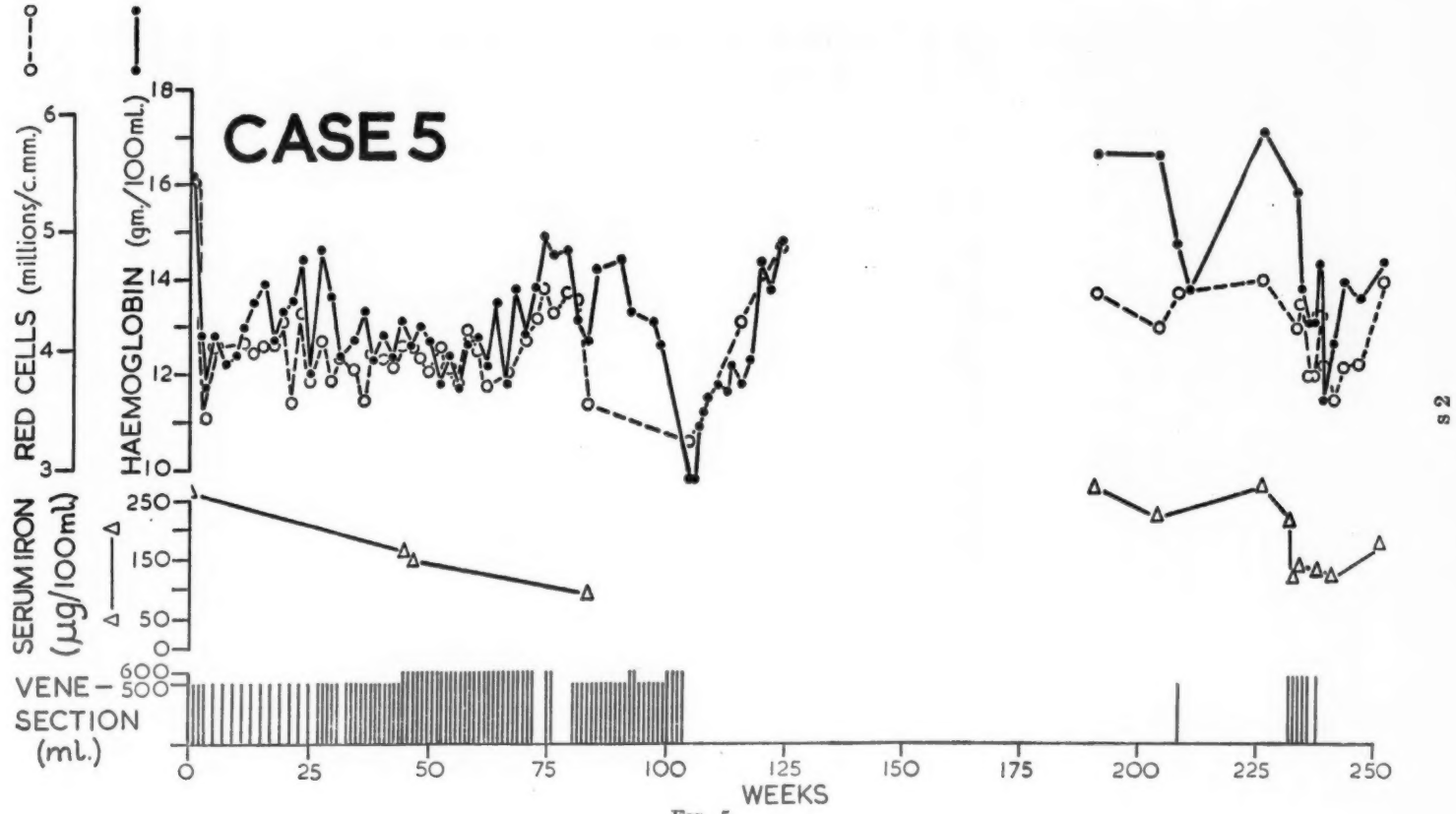
CASE 5
RED CELLS (millions/c.mm.)
HAEMOGLOBIN (gm./100mL.)
SERUM IRON (µg/100ml)
VENE-SECTION (ml.)
WEEKS
0
25
50
75
100
125
150
175
200
225
250
S 2

Fig. 5.

Haematology. The level of haemoglobin and the red-cell count were within normal limits in all cases before treatment (Figs. 1 to 6), but the mean corpuscular volume of red cells was at the upper limit of normal or above (94 to 107 c.μ). In every case, however, the sternal marrow picture was normoblastic. Such a macrocytosis of the peripheral blood has been noted previously in haemochromatosis (Stauffer, Butt, and Dockerty, 1954), and may be related to the

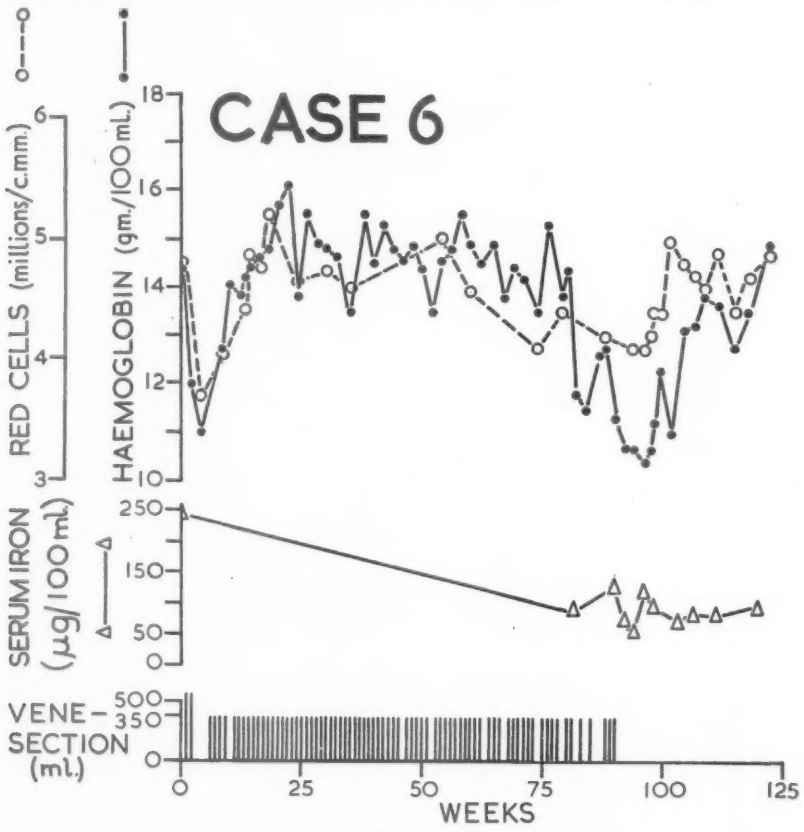

FIG. 6.

associated cirrhosis of the liver (Rosenberg and Walters, 1936; Jarrold and Vilter, 1949). All other aspects of the blood picture were normal in every patient, apart from a reduction in the number of platelets in Case 1 (91,000 per c.mm.) and in Case 6 (110,000 per c.mm.). At the beginning of the course of venesection the haemoglobin level fell slightly in all patients, but returned to normal after eight to 18 weeks, in spite of continued venesection (Figs. 1 to 6). No further significant change occurred for many months, the mean level remaining above 13·5 gm. per 100 ml. in all cases except Case 5, in which it was a little lower. Eventually the level began to fall progressively, and venesection was discontinued when it reached 10 to 11 gm. per 100 ml. The time required to produce

this anaemic state varied from one to four years, and the total volume of blood removed ranged from 16 to 70 litres (Table V). Throughout the course of venesection the red-cell count followed the trend of the haemoglobin level (Figs. 1 to 6). The mean corpuscular volume gradually decreased to within normal limits in most cases. Little change occurred in the packed cell volume until it fell abruptly (to 28 to 38 per cent.) with the development of the anaemia,

TABLE I

Liver Function Tests Before Treatment

Test	*Normal range**	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
Serum-bilirubin (mg./100 ml.)	0·2–1·0	0·5	0·5	0·5	0·5	0·5	0·5
Alkaline phosphatase (King-Armstrong units)	4–12	20	12	20	11	9	5
Serum-proteins† (gm./100 ml.) Total	6·0–8·0	7·7	7·0	7·2	6·8	6·2	6·9
Albumin	3·2–4·4	4·5	3·9	3·8	4·0	3·7	3·9
Globulin	2·8–3·6	3·2	3·1	3·4	2·8	2·5	3·0
Plasma-fibrinogen (gm./100 ml.)	0·2–0·4	0·4	0·3	0·4	0·3	0·4	1·3
Serum colloidal gold turbidity (units)	0–2	0	0	0	0	0	0
Thymol turbidity (units)	0–4	3	4	5	2	4	2
Thymol flocculation (units)	0	0	0	0	0	0	0
Zinc turbidity (units)	0–6	8	5	8	6	4	..
Prothrombin index (%)	75–100	58	69	62	48	78	32
Bromsulphthalein‡ (% retention at 45 min.)	0–5	0	4·5	1·3	0·3	0	4·9
Urine urobilinogen (mg./day)	0–4	0	0	0	19·5	0	0

* Normal range is mean value ± twice the standard deviation.
† Serum-proteins estimated by the method of Wolfson, Cohn, Calvary, and Ichiba (1948).
‡ Dose of bromsulphthalein 5 mg. per kg. body-weight.

and at this time there was also a slight reduction in the mean corpuscular haemoglobin concentration (to 30 to 31 per cent.). The reticulocyte count was not at any time higher than 3 per cent. In Cases 1 and 6 the number of platelets rose to normal.

The liver was considerably enlarged in all cases before treatment. Other clinical manifestations of liver disorder (spider naevi, ascites, and splenomegaly) were not present. Radiological examination in all cases failed to demonstrate oesophageal varices. Laboratory tests of liver function are recorded in Table I. On the whole the results of the tests show only slight impairment of liver function, and this is similar to the findings of other workers (Althausen, Doig, Weiden, Motteram, Turner, and Moore, 1951; Marble and Bailey, 1951; Stauffer, Butt, and Dockerty, 1954). Liver biopsy revealed moderately severe portal cirrhosis and marked haemosiderosis in every patient except one (Case 4), in whom the cirrhosis was slight and the amount of iron-pigment small. As venesection proceeded, the liver diminished in size in every patient, and eventually became impalpable in Cases 1, 2, 4, and 6. Striking reduction occurred in one patient (Case 3), in whom the liver was originally so large and irregular that the presence of a complicating primary carcinoma of the liver had been considered likely (Plate 25, Fig. 8). This patient, in addition, lost the attacks of pain over the liver which had previously troubled him. During and after treatment there was some improvement in the results of liver function tests. The slightly raised

level of serum alkaline phosphatase fell to normal in Case 1. In Case 3 it remained slightly elevated, but the thymol and zinc turbidity tests in this case became normal. The high plasma-fibrinogen value in Case 6 fell to normal by the end of treatment. The low prothrombin index initially present in all patients rose to 100 per cent., and remained so without vitamin K therapy, except in Case 6. In Case 4 the excretion of urobilinogen in the urine continued

TABLE II

Tests of Pancreatic Exocrine Function Before Treatment

Test	*Normal range*	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
Serum-amylase (Somogyi units/100 ml.)	50–160	230	62	133	230	160	266
Serum-lipase (Gömöri units/100 ml.)	15–41	7	21	16	15	12	11
Fat-absorption (%)	92–98	96	98	96	97	86	97
Faecal nitrogen (gm./day)	1·0–2·0	1·9	1·2	1·8	1·3	1·5	..
Duodenal contents after secretin: Total volume (ml.)	99–449	166	148	432	208	242	..
Duodenal contents after secretin: Maximum bicarbonate concentration (mEq./l.)	60–134	104	65	44	144	31	..
Duodenal contents after secretin: Trypsin (greatest activity)	0·02–0*	0·003	..	..	0·003	0·013	..
	0·6–3·2†	..	0·80	0·20	..	..	..

Fat and nitrogen balances were conducted over six-day periods (fat intake 70 gm. per day). Duodenal intubation tests were carried out by the method of Lagerlöf (1942). Volume, bicarbonate concentration, and trypsin activity of duodenal juice were estimated in four successive 20-minute collections after the injection of secretin (1 unit per kg. body-weight of lyophilized secretin made by Wyeth of Philadelphia, U.S.A.). The normal range of values for total volume and maximum bicarbonate concentration are from data published by Dreiling and Hollander (1948).

* Trypsin estimated in Andersen and Early values in ml. (1942).

† Trypsin estimated in international units (Ågren and Lagerlöf, 1936).

raised for most of the period of treatment, but towards the end became normal. Other tests of liver function were repeated a number of times, and the results remained within normal limits. The serum-protein levels kept remarkably constant, in spite of the repeated removal of whole blood without plasma replacement. At the end of therapy, when anaemia had been produced, liver biopsies were repeated in Cases 2, 3, 4, 5, and 6. The sections in all these cases showed a very marked reduction in the haemosiderin-content, the granules being almost absent in both liver-cells and portal tracts (Plate 26, Fig. 9). No special change, however, was detectable in the severity of the accompanying cirrhosis.

Pancreas. (1) Endocrine function. Two patients (Cases 1 and 2) had diabetes mellitus, and both required insulin therapy. The glucose-tolerance curve was normal in Case 4, and of a lag-storage type in Cases 3, 5, and 6. During treatment the daily insulin requirement in Case 1 did not change from 20 units of protamine zinc insulin, but in Case 2 it diminished from 60 to 35 units of globin insulin. After treatment glucose-tolerance tests, repeated in the non-diabetic cases, showed essentially the same form of curve as before.

(2) Exocrine function. The results of tests of function before treatment are

shown in Table II. In several cases the levels of serum-amylase were a little raised, but not to a significant degree. Fat-absorption in Case 5 was slightly below normal, but there was no clinical evidence of steatorrhoea. This patient had a gastroenterostomy, which may have accounted for the impaired absorption. The results of duodenal intubation were normal, except for a low value for the maximum bicarbonate concentration in Cases 3 and 5, and a low trypsin

TABLE III

Radioiodine Tests of Thyroid Function

	Urinary excretion of ^{131}I *% of administered dose in*				*Factor T*	*48-hr. neck uptake of* ^{131}I (%)	*Comment on thyroid function*
	0–8 hrs.	*8–24 hrs.*	*24–48 hrs.*	*0–48 hrs.*			
Normal range*	26·0–49·5	6·6–19·1	0·1–9·4	37·6–68·7	2·72–10·0	25–50	
Case 1:							
(*a*) before treatment	12·9	25·6	12·9	51·4	1·0	8·1	Almost complete failure
(*b*) after T.S.H.†	38·6	28·5	10·1	77·2	1·8	12·2	No response to T.S.H.
Case 2	52·8	12·6	2·5	67·9	6·2	34·4	Normal
Case 3:							
(*a*) before treatment	16·9	26·3	4·1	47·3	1·4	28·5	Defective but not absent
(*b*) after T.S.H.†	23·5	3·5	Nil	27·0	25·0	59·0	A response to T.S.H.
(*c*) after course of venesection	28·7	14·9	7·2	50·8	3·8	..	Normal
Case 4	49·3	19·6	5·3	74·2	3·4	16·9	Low normal
Case 5	31·8	19·0	6·0	56·8	3·0	..	Normal
Case 6	33·0	19·7	8·2	60·9	2·8	..	Low normal

In Cases 2, 4, 5, and 6 the results are from tests carried out before treatment. When the tests were repeated after the course of venesection the results were again normal.

* Fraser, Hobson, Arnott, and Emery (1953).

† Thyroid stimulating hormone (T.S.H.) was given as 'ambinon B' 2 ml. intramuscularly every day for six days before the test.

activity in Case 3. The above tests indicated that exocrine function was not impaired in any case to more than a slight degree, and this is in agreement with the findings of Althausen, Doig, Weiden, Motteram, Turner, and Moore (1951), who used similar methods of investigation. During treatment the serum-amylase and serum-lipase levels were followed serially, and no significant change was observed. In Case 5 the fat balance was repeated after two years' treatment, and absorption had then risen to 95 per cent. No clinical manifestations of pancreatic disorder developed during treatment, and the more elaborate tests of function were not repeated.

Thyroid. There was no clinical evidence of disturbed thyroid function before treatment in any patient except one (Case 1), who had symptoms and signs of myxoedema. The results of radioiodine tests with ^{131}I (Table III) indicated a much depressed function of the gland, as expected, in Case 1, but also slightly defective function in Case 3. These two patients were given a course of thyrotrophic hormone, after which the radioiodine tests were repeated (Table III). The results were unchanged in Case 1, demonstrating that the defect of function was confined to the thyroid gland. In Case 3 the hyperthyroid response indicated that most of the depression of thyroid function was related to anterior pituitary failure (Perloff, Levy, and Despopoulos, 1951). Other tests of anterior pituitary function were normal in this case (Robinson-Power-Kepler water load, 17-ketosteroid excretion, and insulin-sensitivity). As haemosiderosis and fibrosis

of the thyroid gland so often occur in haemochromatosis, disturbance of thyroid function might be expected to be a common feature. Sheldon (1935), however,

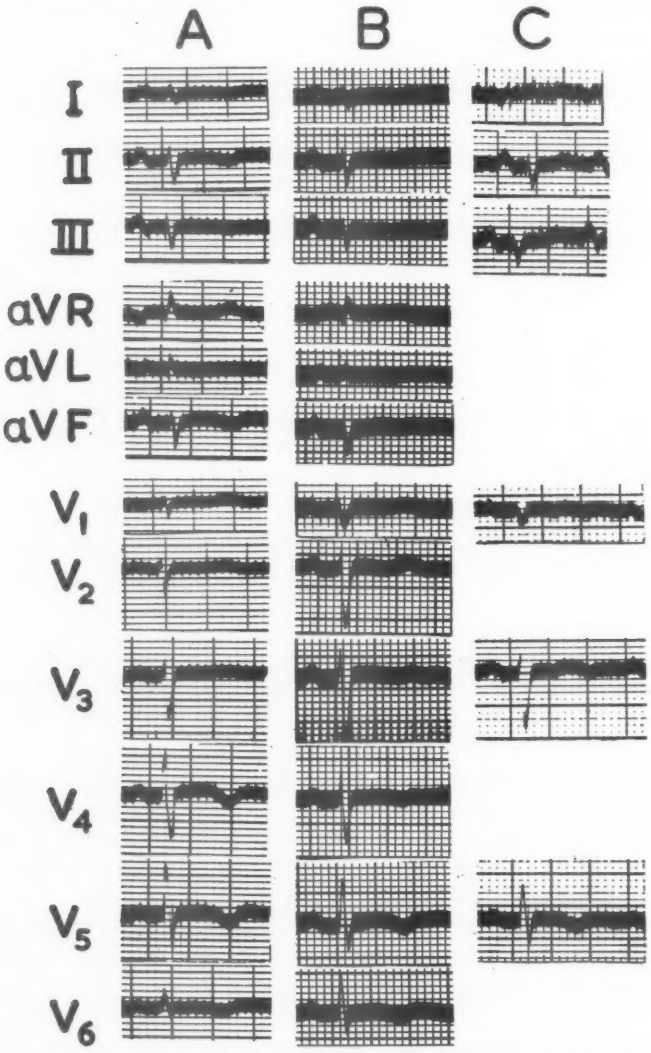

FIG. 7. Case 6. (A) Electrocardiogram before treatment. The voltage of the QRS complexes is low, and the T waves are flat or inverted. (B) Electrocardiogram after treatment. The tracings are similar to those taken before treatment. (C) Electrocardiogram after exercise. No alteration has appeared.

commented on the remarkable absence of clinical evidence of thyroid disturbance. We have found only one previous report clearly describing hypothyroidism occurring in haemochromatosis (Darnall, 1935), and in this case the depression

of function was considered to be secondary to pituitary deficiency. In Case 1 the patient was treated with *l*-thyroxine, 0·3 mg. daily, and lost all evidence of myxoedema. By the end of the course of venesection the daily requirement of *l*-thyroxine had dropped to 0·2 mg. In Case 3 no thyroid drugs were given, and at the end of the venesection treatment the radioiodine urinary excretion test was repeated (Table III), with a normal result, indicating improved thyroid and pituitary function.

Heart. Before treatment evidence of cardiac impairment was found only in Case 6, except for the changes due to myxoedema in the electrocardiogram of Case 1. In Case 6 the patient had congestive cardiac failure. There was a history of increasing breathlessness on exertion for the previous 12 months, and swelling of the feet for two months. Investigation of the heart did not indicate the presence of any cause other than involvement of the myocardium by haemochromatosis (see Appendix). The electrocardiogram showed low-voltage QRS complexes and flat or inverted T waves (Fig. 7A), which are the usual findings in haemochromatosis with cardiac involvement (Bothwell and Alper, 1951). During and after the period of venesection no change occurred in the cardiovascular system in Cases 1, 2, 3, 4, or 5. In Case 6, one month after the patient's admission to hospital, the signs of congestive cardiac failure had cleared, but breathlessness still occurred on slight exertion. At this time all cardiac drugs were stopped, and the course of venesection was started. The patient's exercise tolerance steadily improved, and after a further month he was sent home. Two months later he returned to full-time work, and was able to walk up 30 stairs without undue breathlessness. During the next 12 months the exercise tolerance further improved. The course of venesection was completed after two years, and during this period there was at no time any evidence of returning heart failure. The size of the heart on radiography remained unchanged. Serial electrocardiograms showed persistence of the original abnormalities (Fig. 7B). Exercise had no effect on these changes (Fig. 7C), and this finding indicated that coronary artery disease was unlikely to be the underlying cause. Thyroxine was given for six weeks (0·1 mg., 0·2 mg., and 0·3 mg. daily, each dose being given for two weeks) and this also had no effect on the electrocardiogram. All the evidence indicated that haemochromatosis was the cause of the original heart failure.

Serum-iron levels. Before the commencement of treatment the high values of serum-iron characteristic of haemochromatosis (Frandsen, 1947) were present in every case (Table IV). The serum iron-binding capacities (Cases 1 to 5) were completely or almost completely saturated, as is expected in this disease (Rath and Finch, 1949; Houston and Thompson, 1952). During the course of venesection the serum-iron levels fell in all cases, and became normal when the anaemic state developed (Figs. 1 to 6).

Progress after the course of venesection. The period of follow-up after the course of venesection has been eight months in Cases 3 and 6, and between two and four years in the remainder. At the time of completing the course the phosphate mixture was discontinued, and the diet was changed to one of normal iron-content (10–25 mg. per day). All the patients have remained in good health,

but minor symptoms have persisted in Case 4. Physical examination and liver function tests have shown no further change. Recovery from the anaemia occurred after varying periods: 18 weeks in Cases 2, 3, 5, and 6, 12 months in Case 1, and four years in Case 4 (Figs. 1 to 6). After the disappearance of the anaemia the serum-iron and the mean corpuscular volume tended to return to abnormally high levels. In Case 4 the prolonged anaemia (mean corpuscular

TABLE IV

Serum-Iron Estimations Before Treatment

Case number	*Serum-iron level (μg./100 ml.)*	*Iron-binding capacity (μg./100 ml.)*
1	255	249
2	243	239
3	240	251
4	293	303
5	257	256
6	248	..
Normal range	76–158	249–387

Serum-iron levels and iron-binding capacities estimated by the methods of Davies, Levin, and Oberholzer (1952).

haemoglobin concentration 29 to 32 per cent.; mean corpuscular volume 82–94 c.μ) was treated with ascorbic acid, vitamin B_{12}, and folic acid, without effect. Iron therapy was withheld, but a blood transfusion (500 ml.) was given on two occasions, with a little improvement (Fig. 4). No cause could be found for the anaemia, but a partial gastrectomy had been performed 10 years previously, and it is possible that this had reduced the patient's capacity to absorb iron.

It is not to be expected in haemochromatosis that the underlying disorder of excessive iron absorption (2 to 4 mg. per day) would be modified by a course of venesection. This being so, the rate of reaccumulation of iron stores would be 0·75 to 1·5 gm. per year. It was decided to try the effect of maintenance venesection in those of our patients who had maintained their recovery from the anaemia for one year or longer (Cases 1, 2, and 5). Weekly bleeding of 500 ml. was carried out, until a mild anaemia again developed together with a fall in the level of serum-iron (Figs. 1, 2, and 5). The total amount of iron it was necessary to remove to achieve this state corresponded to a reaccumulation of 0·6 gm. of iron per annum in each case. Recovery from this second anaemic state took place after 30 weeks in Case 1, seven weeks in Case 2, and 14 weeks in Case 5.

Discussion

Since Davis and Arrowsmith (1952) first described their experiences in treating haemochromatosis by repeated venesection, a number of other accounts have been published. Listed in Table V are our own six cases, together with those which have previously been reported in adequate detail and in which the

iron stores have been significantly reduced. At the beginning of the course of venesection some of these patients showed a transient anaemia, but subsequently all showed a remarkable ability to manufacture haemoglobin and red blood-cells over a period of many months. Outstanding is Case G. P. of Davis and Arrowsmith; from this patient 50 litres of blood were taken in 60 weeks without reducing the haemoglobin level. In the patient of Davey, Foxell, and Kemp

TABLE V

Recorded Cases of Treatment of Haemochromatosis by Repeated Venesection

Authors	*Case*	*Age (years)*	*Sex*	*Total venesection (litres)*	*Duration of course of venesection (months)*	*Total iron removed (gm.)*
Davis and Arrowsmith (1952, 1953)	P. S.*	69	F	40	22	20
	A. W.*	45	M	40	16	20
	G. P.*	47	M	51	21	26
Peterson and Ettinger (1953)	1*	50	M	37	14	15
Warthin, Peterson, and Barr (1953)	..	57	M	30	36	15
Howard, Balfour, and Cullen (1954)	2	43	M	96	47	45
Davey, Foxell, and Kemp (1954)	..	55	M	31	24	15
Pirart and Carpent (1955)	L. P.*	69	M	31	28	12
	G. A.*	46	M	48	28	20
Myerson and Carroll (1955)	R. B.*	34	M	40	28	20
Finch and Finch (1955)	E. M.	47	M	?	30	26
McAllen, Coghill, and Lubran (1957)	1	53	M	34	34	17
	2*	48	M	44	24	21
	3*	48	M	70	53	32
	4*	46	M	16	11	7
	5*	58	M	46	23	21
	6*	54	M	27	21	13

* Liver biopsy repeated.

In our patients the amount of haemoglobin in the blood removed was estimated at each venesection, and the iron-content calculated on the assumption that 100 gm. of haemoglobin contains 0·334 gm. of iron.

(1954), the two patients of Pirart and Carpent (1955), Case 1 of Peterson and Ettinger (1953), and our own six patients, a state of anaemia was produced eventually, and by this time the serum-iron level was falling to normal. Evidence that venesection had much reduced the stores of iron in the body was shown by the marked diminution or complete disappearance of haemosiderin from the subsequent liver biopsy specimens from the patients in whom this procedure was carried out. The total amount of iron it was found necessary to remove for effective reduction of iron stores in the body varied from 7 to 45 gm.

No complications or ill effects followed regular venesection in our patients. The replacement of plasma-proteins, recommended by Davis and Arrowsmith (1952), was not found to be necessary with the patients taking a diet of adequate protein and calorie content. Blood removal was limited to a rate of 350 to 600 ml. each week, and on this régime our patients were able to continue their normal work. It was considered that the more intensive régimes of other workers

would have interfered with wage-earning, and would have made co-operation by our patients unlikely over the long periods required for treatment.

All the patients listed in Table V, except Case 1 of Peterson and Ettinger and the two patients of Pirart and Carpent, derived clinical benefit from the course of venesection. There occurred an increased sense of well-being, and usually a reduction in the size of the liver and an improvement shown by liver-function tests. In some cases skin pigmentation lessened, hypogonadism improved, and insulin requirements diminished. Among our patients the least symptomatic improvement occurred in Case 4, but this patient had the smallest iron deposits, and probably few of his symptoms were related to haemochromatosis. The reduced *l*-thyroxine requirements in Case 1, and the improved results of thyroid tests in Case 3, suggest that venesection also improved the thyroid and anterior pituitary function in these patients.

The occurrence of congestive cardiac failure in our Case 6 is of considerable interest. All the facts indicate that the cause of the failure was haemosiderosis of the heart muscle, associated with muscle damage and fibrosis. Cardiac failure is one of the worst complications of haemochromatosis, because, despite any initial improvement on standard treatment with rest, digitalis, and diuretics, death nearly always occurs within one year of the onset of failure (Bothwell and Alper, 1951; Bothwell, van Lingen, Alper, and du Preez, 1952). In our patient the signs of congestive cardiac failure gradually cleared during a period of three months with rest, digitalis, and mersalyl, but slight exertion still produced breathlessness. After the venesection course was started, however, the exercise tolerance steadily and markedly improved, even though all cardiac drugs were stopped. The electrocardiogram has remained abnormal, and this is probably due to permanent fibrosis of the myocardium. Nearly three years after the onset of the congestive cardiac failure the patient is well and working full-time. The hope has been expressed by a number of authors that treatment by venesection will improve the prognosis in cases of heart failure, although it has been feared that these patients may not stand up to the strain of such a procedure. As far as we are aware, Case 6 is the first fully reported case in which this treatment has been used in haemochromatosis with heart failure. The result seems to justify the hope expressed, and the good response suggests that venesection therapy is an urgent requirement in these cases.

After completing the course of venesection, some form of maintenance therapy is likely to be required in all cases in order to keep the iron stores in the body at a reasonably low level. For this purpose the use of a low-iron diet, phosphate administration, or further venesection may be considered. The two former methods, as previously mentioned, are without practical value. Further venesection at intervals has therefore been used in three of our patients. The response indicated that removal of one to two litres of blood (0·5 to 1·0 gm. of iron) per annum counteracted the reaccumulation of iron.

The evidence up to date is that reduction of the iron stores in haemochromatosis by repeated venesection results in arrest of progress of the disease, relief of symptoms, and improvement in function of some of the affected organs. The

tissue fibrosis frequently present in these organs is probably not lessened by the removal of iron, but such fibrosis, particularly in the liver, is not incompatible with long life. All our patients have exceeded the expectation of life for their condition, but follow-up of a large number of treated patients is required before it can be known definitely whether the long-term prognosis of haemochromatosis can be improved by this form of treatment.

We wish to thank Dr. Donald Hunter, of the London Hospital, for permission to record the early details of Case 2, Dr. D. McCarthy, general practitioner, for referring Case 6 to us, and our colleague Dr. M. M. Deane for referring Case 4. We are greatly indebted to Dr. Russell Fraser, of Hammersmith Hospital, for carrying out some of the tests of thyroid function and for help in the interpretation of these tests. We are grateful to Dr. B. Levin, of Queen Elizabeth Hospital for Children, Hackney, for performing the iron estimations recorded in Table IV. Our thanks are also due to Mr. D. A. Vinten for the coloured photomicrographs.

APPENDIX

I. *Case Reports*

In each of the six cases a normal diet (including iron, phosphate, and vitamin content) had always been taken and the consumption of alcohol had never been excessive. No patient had received iron therapy or blood transfusions. There were no other known cases of haemochromatosis in their families.

Case 1. H. C., an engine-driver aged 53 years, was first seen in November 1950 with a history of six months of increasing thirst, polyuria, loss of weight, and misty vision, and 12 months of weakness, easy fatigue, deafness, mental slowness, and intolerance of cold. Libido had been absent for three years. Daily shaving was required. Physical examination revealed slight myxoedema, and a light brown pigmentation of the face, neck, forearms, and shins The thyroid gland was not palpable. Hair distribution was masculine in type, and the external genitalia were normal. The liver was firm, smooth, and enlarged to four fingers' breadth below the costal margin. The blood-pressure was 140/70. The fasting blood-sugar was 284 mg. per 100 ml. A skin biopsy did not show any iron pigment. The sternal bone-marrow did not reveal any increase in the number of iron-containing granules. Urinary sediment was free from haemosiderin granules on repeated examination. The fasting gastric juice contained free acid. The blood Wassermann and Kahn reactions were negative. The Van Slyke urea clearance test showed a maximum clearance of 98 per cent. of the average value. Radiological examination of the heart and lungs was normal. An electrocardiogram showed low voltage of T waves in both standard and chest leads. The serum-cholesterol was 537 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 141; chloride 98; potassium 4·4; phosphorus 1·7; calcium 6·2. The Cutler-Wilder-Power test of adrenal function was normal (urinary chlorides 48 mg. per 100 ml.). The 17-ketosteroid excretion in the urine was 9·2 mg. per day. A sample of seminal fluid indicated poor testicular function (volume of ejaculate 0·75 ml.; liquefaction incomplete; azoospermia).

Family history. The patient's father is well and 86 years old; his mother died

of anaemia at 64 years of age. He has five brothers, four sisters, four daughters, and six grandsons, who are all alive and well.

Case 2. D. H., a water-board engineer aged 48 years, developed the symptoms of diabetes in 1937, and was treated with insulin. In 1944 the diabetes became more severe; he was admitted to the London Hospital under the care of Dr. Donald Hunter, and at this time the presence of haemochromatosis was recognized. He was first seen at the West Middlesex Hospital in May 1950, when he had an attack of acute gastroenteritis. Libido had been absent for some years, and he was easily fatigued. All his adult life he had shaved only on alternate days. Physical examination showed a grey-brown colour in the skin of the face, neck, forearms, and shins. The body-hair was scanty and feminine in distribution, and the testes were very small and soft. The liver was firm, smooth, and enlarged to five fingers' breadth below the costal margin. The blood pressure was 140/80. The fasting blood-sugar was 314 mg. per 100 ml. A biopsy of the skin did not show any iron pigment. The sternal bone-marrow revealed the presence of numerous haemosiderin granules in the reticulo-endothelial cells. A gastric biopsy showed numerous deposits of iron in the mucosa. Urinary sediment was free from haemosiderin granules. The fasting gastric juice contained no free acid before or after the injection of 0·5 mg. histamine phosphate. The blood Wassermann and Kahn reactions were negative. The Van Slyke urea clearance test showed a maximum clearance of 101 per cent. of the average value. An X-ray of the chest showed a normal heart and clear lung fields. The electrocardiogram was normal. The serum-cholesterol was 310 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 140; chloride 95; potassium 5·0; phosphorus 2·5; calcium 4·5. The Robinson-Power-Kepler water-load test was normal. The Cutler-Wilder-Power test of adrenal function was within normal limits (urinary chlorides 199 mg. per 100 ml.). The 17-ketosteroid excretion in the urine was 3·7 mg. per day. The patient was unable to ejaculate semen.

Family history. The patient's father died from high blood-pressure at 65 years, and his mother from diabetes at 57 years of age. He has a twin brother (not identical), one younger brother, and an adult son and daughter. The younger brother has a slightly raised level of serum-iron (169 μg. per 100 ml.), but is normal on physical examination. The other members of the family have serum-iron levels within normal limits.

Case 3. G. S., a factory hand aged 48 years, first attended hospital in September 1950 with a recent history of attacks of pain in the region of the liver, and a nine months' history of general weakness, easy fatigue, and loss of weight. His libido was normal. All his adult life shaving had been required only three days each week. Physical examination showed a generalized grey-brown colour in the skin. The hair distribution and external genitalia were normal. The liver was hard, tender, and a little irregular, and so enlarged that the lower border reached the level of the anterior superior iliac spines. The blood-pressure was 120/80. A skin biopsy showed iron pigment to be present. Fishbach's ferrocyanide skin test was negative. The sternal bone-marrow did not reveal any increase of iron-containing granules. A gastric biopsy specimen contained iron deposits. Urinary sediment was free from haemosiderin granules. The fasting gastric juice contained free acid. The blood Wassermann and Kahn reactions were negative. The Van Slyke urea clearance test showed a maximum clearance of 99 per cent. of the average value. The chest, stomach, and gall-bladder were normal on radiological examination. The electrocardiogram was normal. The serum-

cholesterol was 287 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 142; chloride 98; potassium 4·9; phosphorus 3·1; calcium 6·4. The Robinson-Power-Kepler water-load test was normal. The Cutler-Wilder-Power test of adrenal function was normal (urinary chlorides 99 mg. per 100 ml.). The 17-ketosteroid excretion in the urine was 5·9 mg. per day.

Family history. The patient's father died at 68 years, and his mother at 62 years of age, from unknown causes. He has a brother, two sisters, and a daughter. One of the sisters has diabetes mellitus; the other members of the family are well.

Case 4. H. P., a bank clerk aged 46 years, first attended hospital in June 1946 with a 20 years' history of epigastric pain. Barium-meal examination revealed a duodenal ulcer. There was no response to medical treatment, and in June 1948 a partial gastrectomy was performed. After operation epigastric pain still occurred, together with heavy sensations in the stomach, mental depression, headaches, and loss of energy. His libido was normal. Daily shaving was required. In February 1951 a laparotomy was carried out by Mr. J. Scholefield, and the liver was found to be moderately enlarged, dark in colour, and cirrhotic. A biopsy specimen was taken, and revealed haemochromatosis. Physical examination showed a light grey colour in the skin of the face and forearms. The body-hair and external genitalia were normal. The lower edge of the liver was palpable two fingers' breadth below the costal margin. The blood-pressure was 140/90. A skin biopsy did not show any iron pigment. The sternal bone-marrow did not show any increase in the number of iron-containing granules. The urinary sediment was free from haemosiderin granules. The fasting gastric juice contained free acid. The blood Wassermann and Kahn reactions were negative. The Van Slyke urea clearance test showed a maximum clearance of 71 per cent. of the average value. The heart and lungs were normal on radiological examination. The electrocardiogram was normal. The serum-cholesterol was 278 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 143; chloride 99; potassium 4·7; phosphorus 1·9; calcium 5·8. The Cutler-Wilder-Power test of adrenal function was normal (urinary chlorides 31 mg. per 100 ml.). The 17-ketosteroid excretion in the urine was 12 mg. per day. A sample of seminal fluid suggested that testicular function was slightly reduced (volume of ejaculate 1·0 ml.; liquefaction incomplete; acid phosphatase 5,880 King-Armstrong units per 100 ml.; alkaline phosphatase 24 King-Armstrong units per 100 ml.; fructose 100 mg. per 100 ml.; density 14,600,000 per ml.; morphology, 52 per cent. normal forms).

Family history. The patient's father died from cerebral haemorrhage at 49 years, and his mother from angina at 71 years of age. His only brother was killed in an accident at 27 years of age. He has a sister and two sons, who are alive and well.

Case 5. S. T., a window-cleaner aged 58 years, was first seen in 1947 for a minor attack of coronary thrombosis, from which he made a good recovery. At this time the liver was noted to be enlarged. In March 1950 he was admitted for surgical treatment of a chronic duodenal ulcer, which had caused indigestion for many years. A gastrojejunostomy was performed by Mr. J. Scholefield, and a biopsy of the liver established the presence of haemochromatosis. In 1951, because of reduced energy, he could work only part-time. His libido was diminished. All his adult life he had shaved only on alternate days. Physical examination revealed a fine brown pigmentation of the face, forearms, and shins. The body-hair was slightly diminished, but the external genitalia were normal.

The liver was smooth, and enlarged to four fingers' breadth below the costal margin. A skin biopsy showed iron pigment to be present. Fishbach's ferrocyanide test was negative. The sternal bone-marrow revealed an increase of haemosiderin granules in the reticulo-endothelial cells. The urinary sediment was free from haemosiderin granules. The fasting gastric juice contained free acid. The blood Wassermann and Kahn reactions were negative. The Van Slyke urea clearance test showed a maximum clearance of 108 per cent. of the average value. An X-ray of the chest showed a normal heart and clear lung fields. The electrocardiogram was normal. The serum-cholesterol was 162 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 143; chloride 96; potassium 4·5; phosphorus 2·2; calcium 5·0. The Cutler-Wilder-Power test of adrenal function was within normal limits (urinary chlorides 51 mg. per 100 ml.). The 17-ketosteroid excretion in the urine was 9·8 mg. per day. A sample of seminal fluid did not show any marked abnormality except a low fructose content (volume of ejaculate 1·5 ml.; liquefaction complete; acid phosphatase 7,660 King-Armstrong units per 100 ml.; alkaline phosphatase 160 King-Armstrong units per 100 ml.; fructose 42 mg. per 100 ml.; density 112,000,000 per ml.; morphology, 50 per cent. normal forms).

Family history. The patient's father died from chronic alcoholism at 67 years, and his mother from senility at 71 years of age. One brother died at operation, and one sister in childbirth. The patient has one brother, six sisters, four adult sons, and three adult daughters, who are all alive and well.

Case 6. E. D., a draughtsman aged 54 years, consulted his general practitioner for the first time in early October 1953. During the previous 12 months breathlessness on exertion had steadily increased in severity, and for one week the legs had been swollen. Examination revealed congestion of the neck veins, marked oedema of the feet and legs, an apical systolic murmur, and crepitations at both lung bases. Rest in bed, digoxin 0·25 mg. twice daily, and mersalyl injections were prescribed. Although improvement occurred, the rate of progress was very slow, and after seven weeks the patient was referred to hospital. An additional history was obtained of indigestion for 20 years, shaving only on alternate days for 15 years, loss of libido for 10 years, and easy fatigue for five years. On physical examination he showed a brown pigmentation of the face, hands, forearms, legs, and feet. Hair was absent from the axillae, and scanty over the pubes. The testes were small and soft. The liver was smooth, firm, and enlarged to four fingers' breadth below the costal margin. The neck veins were filled to a level 1 cm. above the sternal angle, and there was moderate oedema of the ankles. The heart rate was normal, and the rhythm regular. No ventricular enlargement was detected. No murmurs were heard, but a presystolic gallop rhythm was present at the apex. The blood-pressure was 120/80. Fluoroscopy revealed a normal cardiac outline except for slight enlargement of the left ventricle. The electrocardiogram showed low-voltage QRS complexes and flat or inverted T waves in the standard and chest leads. A skin biopsy showed iron pigment to be present. Fishbach's ferrocyanide skin test was negative. The sternal bone-marrow revealed the presence of numerous haemosiderin granules in the reticulo-endothelial cells. A gastric biopsy showed iron deposits in the mucosa. Urinary sediment was free from haemosiderin granules. The fasting gastric juice contained free acid. The blood Wassermann and Kahn reactions were negative. A barium examination demonstrated a chronic duodenal ulcer. The Van Slyke urea clearance test showed a maximum clearance of 67 per cent. of the average value. The serum-cholesterol was 319 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 130;

chloride 94; potassium 5·1; calcium 4·8. The Robinson-Power-Kepler water-load test was normal. The Cutler-Wilder-Power test of adrenal function was normal (urinary chlorides 130 mg. per 100 ml.). The urine 17-ketosteroid excretion was 2·6 mg. per day.

No common cause of heart failure was present. There was no history of rheumatism, diphtheria, or angina, and no signs of congenital defects, valvular lesions, pericardial disease, hypertension, thyroid malfunction, anaemia, pulmonary disease, syphilis, malnutrition, or electrolyte upset. Evidence was also lacking of any rare cause of heart failure, such as scleroderma, familial cardiomegaly, and Friedreich's ataxia or other neuromuscular disorders. The patient had never been exposed to tropical diseases. Involvement of the myocardium by haemochromatosis seemed to be the only cause for the heart failure.

Family history. The patient's father died from cancer at 73 years, and his mother from dropsy at 58 years of age. One brother was killed during the Second World War. He has two other brothers, who are alive and well.

II. *Method of Determination of Total Serum Iron Using Nitroso R Salt*

Nitroso R Salt (1-nitroso-2-hydroxy-3, 6-naphthalene disodium sulphonate) has been used by van Klooster (1921) and Sideris (1937, 1942; Sideris, Young, and Chun, 1944) for the determination of ferrous iron, with which it forms a green-coloured complex. This reagent has proved suitable for the determination of iron in blood.

Procedure. All glassware must be iron-free.

To 1 ml. of serum add 1 ml. of dilute hydrochloric acid (1 vol. A.R. conc. HCl+30 vols. distilled water) and incubate at 37° C. in a stoppered tube for two hours, and then treat with 2 ml. of 10 per cent. A.R. trichloracetic acid. Mix by tapping, leave to stand for not less than two hours, preferably overnight, and centrifuge. Treat 2 ml. of the supernatant with 0·2 ml. dilute ammonia (1 vol. 0·880 ammonia+7 vols. distilled water), 0·2 ml. 20 per cent. A.R. hydroxylamine hydrochloride, 0·4 ml. of 0·5 per cent. nitroso R salt, and finally 0·8 ml. of 33 per cent. A.R. sodium acetate. A blank containing water instead of blood is put through the process, as well as a standard containing 5 μg. ferric iron per ml. The colours produced are stable for at least 48 hours, and Beer's law is obeyed at least up to concentrations of 10 μg. per ml. The colours are best read in a photoelectric spectrophotometer at a wave-length of 665 mμ.

Summary

1. The treatment of haemochromatosis is discussed, and the results in six patients treated by repeated venesection are presented.

2. Large amounts of blood were removed without ill effect, and eventually a state of anaemia was produced. By this time the excessive iron stores in the body were almost exhausted, as demonstrated by liver biopsy.

3. Relief of symptoms was obtained in all cases, and an improvement in function of the liver, thyroid, and heart occurred in those cases in which these organs were involved. Insulin requirements decreased in one of the two diabetic patients.

4. After the iron stores in the body had been reduced, it was found that

maintenance venesection of one to two litres per year was required in order to combat reaccumulation of iron.

5. It is considered that the prognosis in haemochromatosis is likely to be much improved by venesection treatment, and that by maintenance therapy the progress of the disease may be arrested.

ADDENDUM

Since this paper was written we have treated one more patient by repeated venesection, and he also has shown improvement. The general results of treatment were that he was no longer easily fatigued, the body-weight increased by 10 kg., skin pigmentation lessened, and there was a return of libido.

Haematology. Before venesection the haemoglobin was 15·2 gm. per 100 ml., red cells 4,700,000 per c.mm., packed cell volume 47 per cent., mean corpuscular volume 100 c.μ, mean corpuscular haemoglobin concentration 32 per cent., and white cells 8,000 per c.mm., with a normal differential count. Sternal puncture showed a normoblastic marrow. Five hundred ml. of blood were removed weekly by venesection, and after 17 months a persistent anaemia developed (10 to 11 gm. per 100 ml.). By this time a total of 32 litres of blood, containing 14 gm. iron, had been removed; the packed cell volume had fallen to 33 per cent., the mean corpuscular volume to 92 c.μ, and the mean corpuscular haemoglobin concentration to 30 per cent.

The liver decreased in size, the lower edge receding from five to two fingers' breadth below the costal margin. Results of liver function tests, abnormal before treatment (plasma-fibrinogen 0·74 gm. per 100 ml.; prothrombin index 60 per cent.), became normal by the end of treatment. The serum-proteins remained constant during the period of venesection. Liver biopsy was repeated, and showed almost complete clearance of the original heavy iron deposits, but no detectable change in the severity of the cirrhosis.

Pancreas. (1) Endocrine function. Glucose tolerance was normal before and after treatment. (2) Exocrine function. Before treatment the serum-amylase was 169 Somogyi units per 100 ml., and fat absorption 97 per cent. No change had occurred by the end of treatment.

Thyroid. There was no clinical evidence of disturbed thyroid function. The radioiodine urinary excretion test gave normal results (0–48 hours excretion, 59 per cent. of dose; Factor T, 3·1) before treatment, and again after treatment.

The cardiovascular system was normal before and after treatment.

The serum-iron before treatment was 273 μg. per 100 ml., and by the end of treatment the level had fallen to 37 μg. per 100 ml.

Clinical details of this case are as follows:

Case 7. P. M., a lorry-driver aged 45 years, was first seen in March 1955, with a four months' history of nervousness, easy fatigue, and poor appetite. For 30 years he had been a heavy beer drinker, but in 1950 he gave this up. In 1951 melaena occurred, and he received two pints of blood by transfusion. Libido had been absent for three years. He shaved daily. The dietary intake had always been normal. Physical examination revealed a generalized grey-brown pigmentation, especially marked on the face, hands, and shins. The body-hair was scanty, with a feminine distribution, and marked gynaecomastia was present. The testes were small and soft. The liver was firm, smooth, and enlarged. The blood-pressure was 145/75. A skin biopsy showed iron pigment to be present. Fishbach's ferrocyanide skin test was faintly positive. The

sternal marrow revealed an increase of haemosiderin granules in the reticulo-endothelial cells. A gastric biopsy showed numerous deposits of iron in the mucosa. The fasting gastric juice contained free acid. The blood Wassermann and Kahn reactions were negative. The Van Slyke urea clearance test showed a maximum clearance of 90 per cent. of the average value. An X-ray of the chest showed a normal heart and clear lung fields. The electrocardiogram was normal. A barium-meal examination revealed a duodenal ulcer. The serum-cholesterol was 260 mg. per 100 ml. The serum-electrolyte values, in mEq. per litre, were: sodium 143; potassium 5·4; phosphorus 2·5; calcium 5·0. The 17-ketosteroid excretion in the urine was 4·9 mg. per day. Examination of a sample of seminal fluid suggested that testicular function was reduced (volume of ejaculate 0·7 ml.; liquefaction complete; acid phosphatase 21,200 King-Armstrong units; fructose 425 mg. per 100 ml.; density 2,000,000 per ml.; morphology, 30 per cent. normal forms).

Family history. The patient's father was killed in the Boer War, and his mother was killed at 70 years of age in an accident. His mother had by a second marriage another son and two daughters, all of whom are alive and well.

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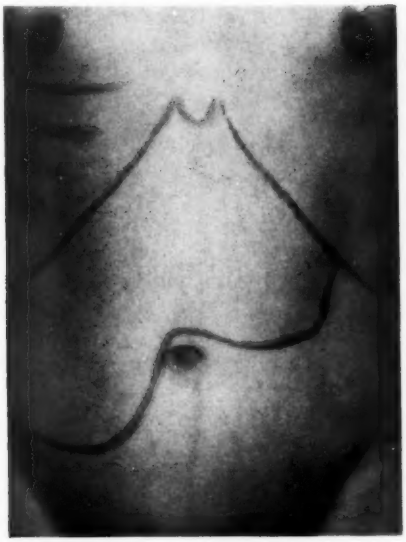


FIG. 8 (*a*)

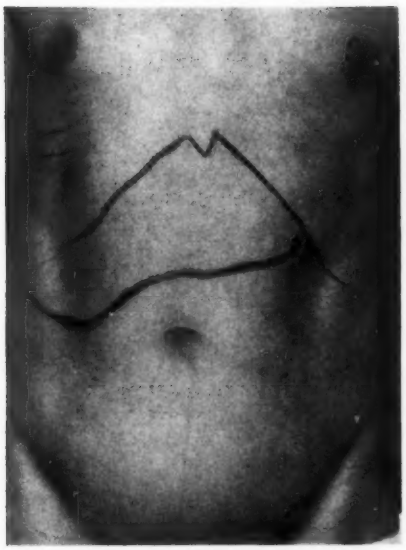
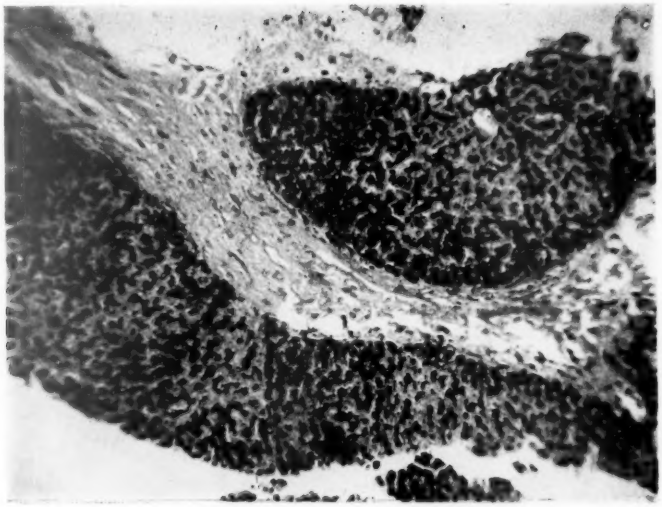
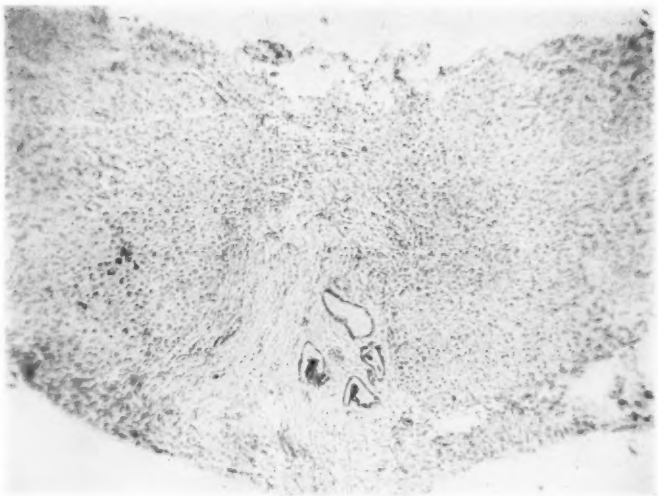


FIG. 8 (*b*)

FIG. 8. Case 3. The size of the liver (*a*) before treatment (May 1951), (*b*) after treatment (November 1955)



(*a*) Before treatment. There are heavy deposits of blue-staining haemosiderin granules in the liver-cells, and small deposits in the portal tracts. Moderately severe portal cirrhosis is also present



(*b*) After treatment. The haemosiderin granules have almost completely disappeared from both the liver-cells and the portal tracts. The severity of the cirrhosis is apparently unchanged

FIG. 9. Case 6. Sections from needle biopsy specimens of liver
(Prussian blue reaction (Gömöri's method), × 56)

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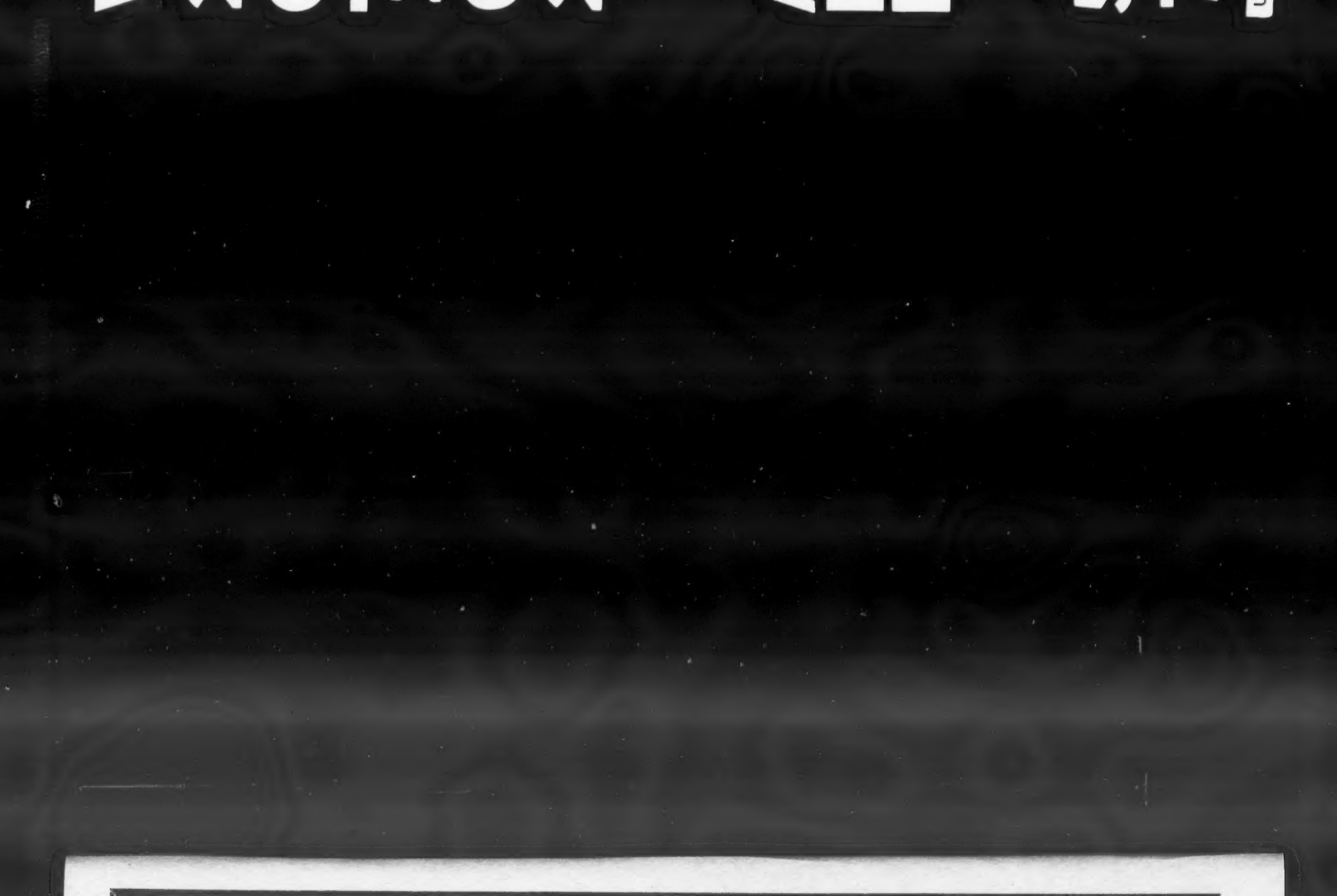
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